VOLUME 107

JANUARY 15

1989

AMERICAN JOURNAL OF OPHTHALMOLOGY

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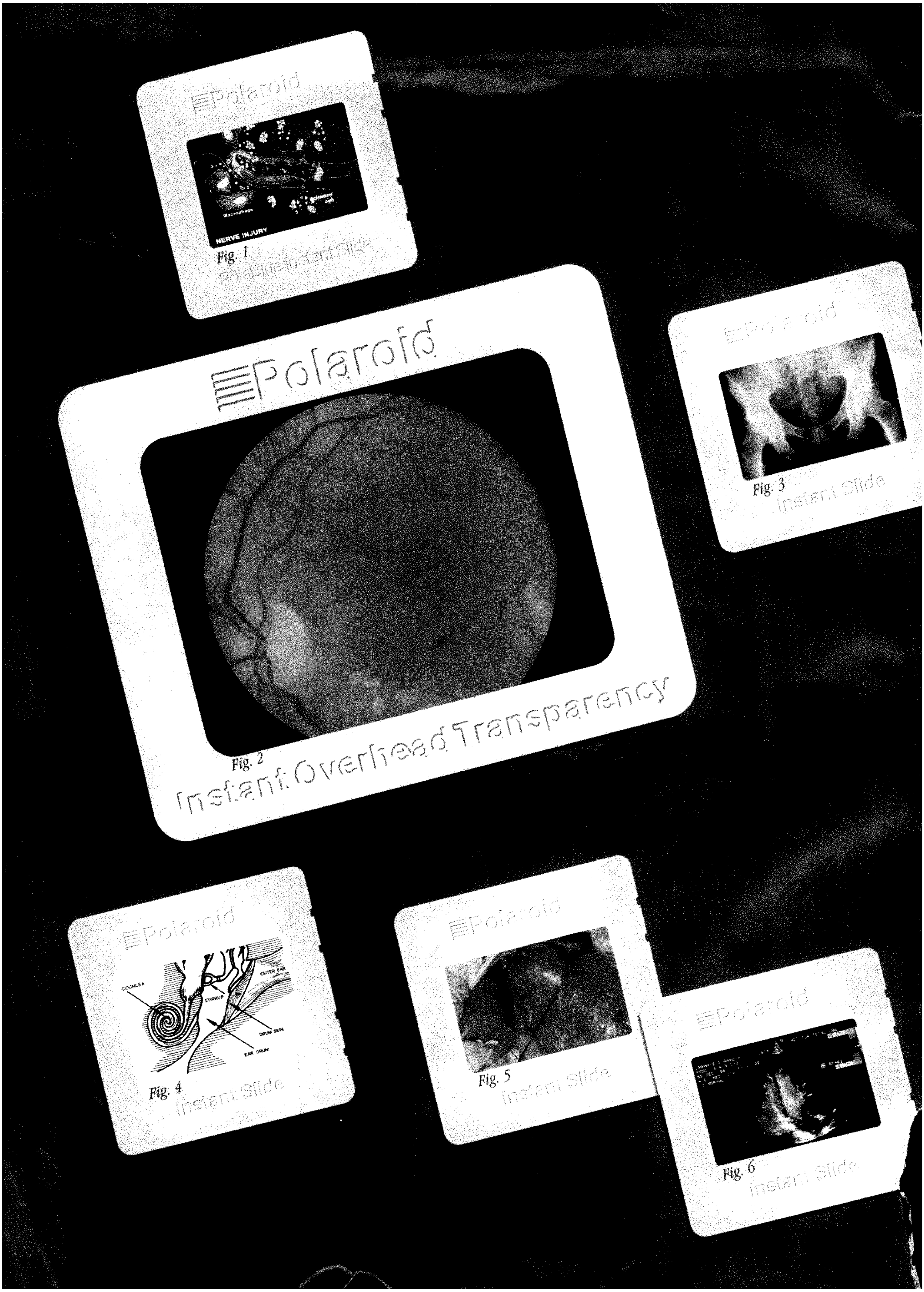

Fig. 1
Fig. 2
Fig. 3
Fig. 4
Fig. 5
Fig. 6

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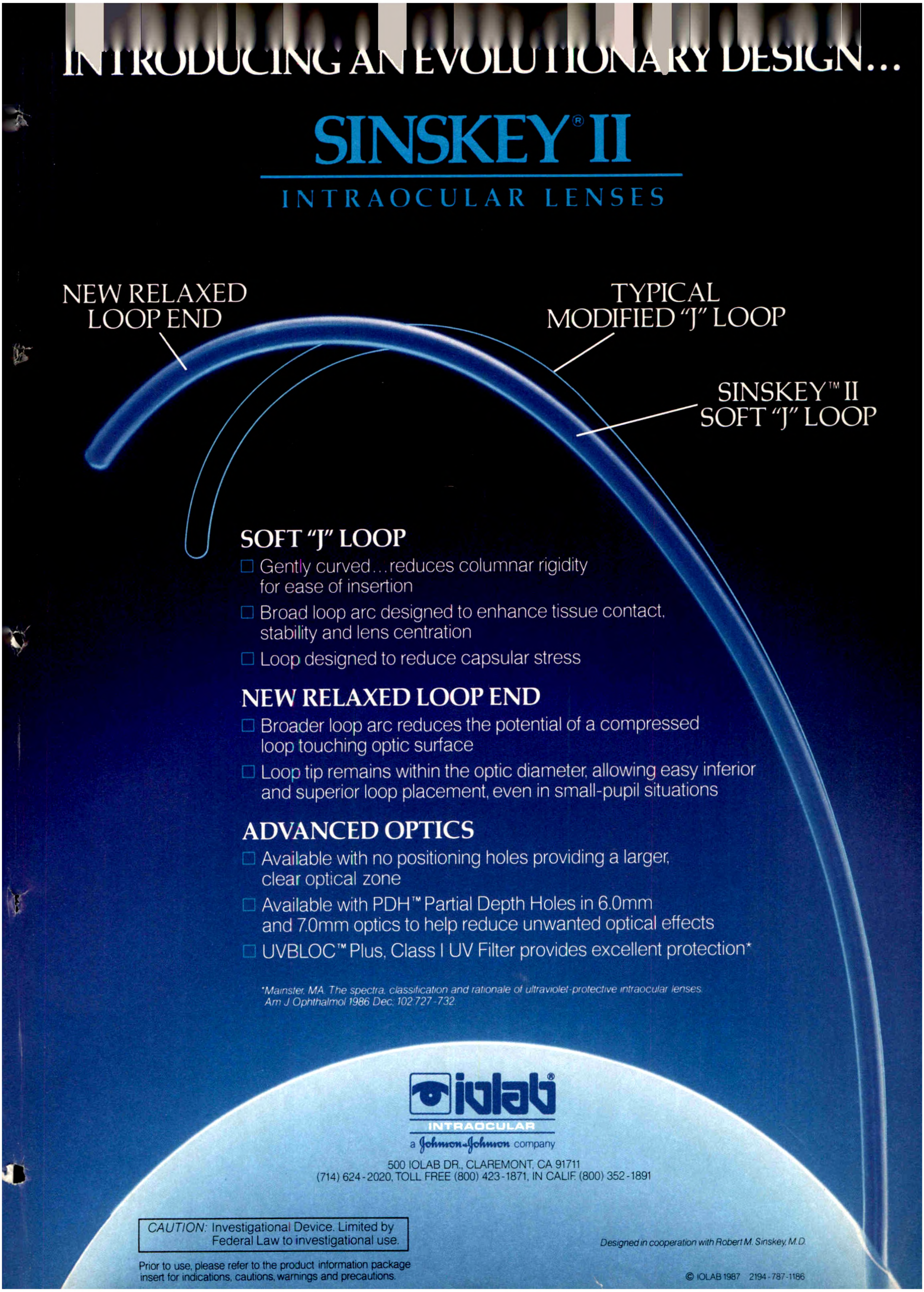
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VISCOAT®

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Summary of Product Information

INDICATIONS: VISCOAT® is indicated for use as a surgical aid in anterior segment procedures including cataract extraction and intraocular lens implantation. VISCOAT® maintains a deep chamber during anterior segment surgeries, enhances visualization during the surgical procedure, and protects the corneal endothelium and other ocular tissues. The viscoelasticity of the solution maintains the normal position of the vitreous face, thus preventing formation of a postoperative flat chamber.

CONTRAINDICATIONS: At the present time, there are no known contraindications to the use of VISCOAT® when used as recommended.

PRECAUTIONS: Precautions are limited to those normally associated with the surgical procedure being performed. Although sodium hyaluronate and sodium chondroitin sulfate are highly purified biological polymers, the physician should be aware of the potential allergic risks inherent in the use of any biological material.

ADVERSE REACTIONS: VISCOAT® has been extremely well tolerated in human and animal studies. A transient rise in intraocular pressure may be expected due to the presence of sodium hyaluronate, which has been shown to effect such a rise (9.8% > 25 mmHg during 1–3 days after surgery in human clinical trials).

HOW SUPPLIED: VISCOAT® is a sterile, non-pyrogenic, 0.25 ml or 0.50 ml, viscoelastic preparation supplied in a disposable syringe (encased in a plastic sheath with a threaded luer tip). A sterile 27-gauge, disposable blunt-tip cannula is provided separately.

FOR INTRAOCULAR USE.
Both VISCOAT® and cannula are for single use only.
Store Between 2°–8°C (36°–46°F). Do Not Freeze.

CAUTION: Federal law restricts this device to sale by, or on the order of, a licensed physician.

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Revised April 1987

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See ad on inside Cover 2, pg 1

INTRODUCING 6 MINUTE STERILIZATION.

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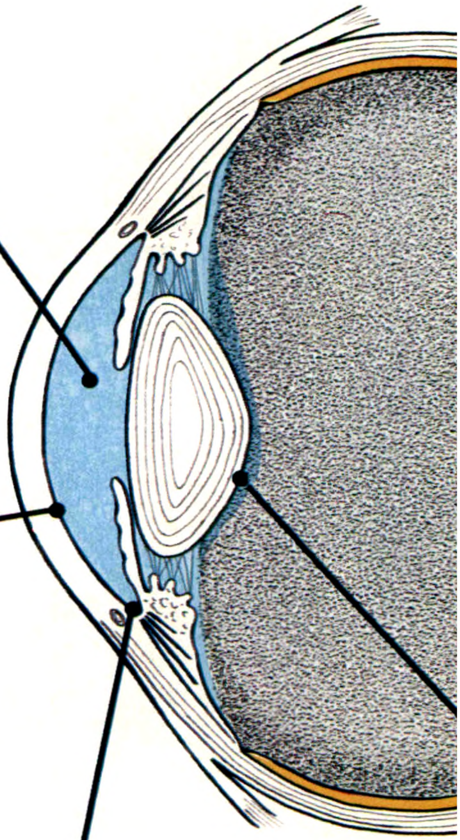
WHERE BSS PLUS® (Balanced Salt Solution Enriched with Bicarbonate, Dextrose and Glutathione) HAS BEEN SHOWN TO PROTECT AND MAINTAIN INTRAOCULAR TISSUES

AQUEOUS HUMOR

	Human Aqueous Humor	BSS PLUS®
Sodium	162.9	160.0
Potassium	2.2-3.9	5.0
Calcium	1.8	1.0
Magnesium	1.1	1.0
Chloride	131.6	130.0
Bicarbonate	20.15	25.0
Phosphate	0.62	3.0
Lactate	2.5	-
Glucose	2.7-3.7	5.0
Ascorbate	1.06	-
Glutathione	0.0019	0.3
Citrate	-	-
Acetate	-	-
pH	7.38	7.4
Osmolality (MO_Sm)	304	305

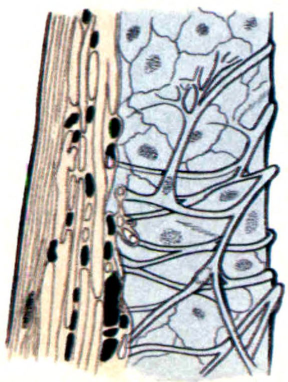
(All concentrations expressed in mmol/L)



CORNEAL ENDOTHELIUM

EDELHAUSER et al (4)
BENSON (2)
GLASSER (5)
KLINE (9)

TRABECULAR MESHWORK

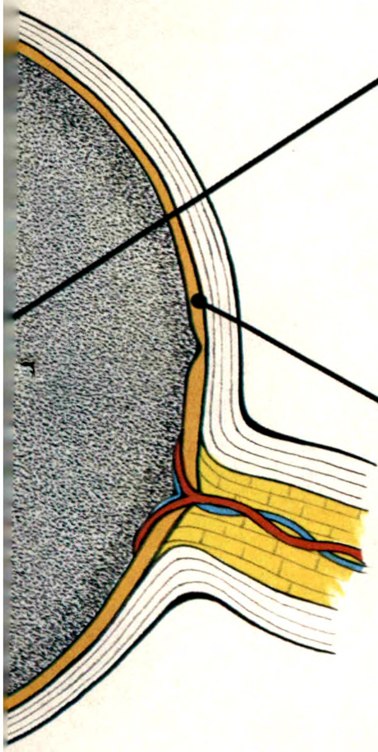


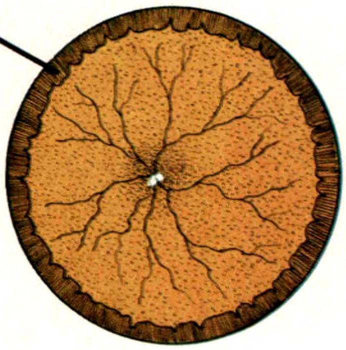
KAHN et al (8)

VITREOUS HUMOR

	Human Vitreous Humor	BSS PLUS®
Sodium	144.0	160.0
Potassium	5.5	5.0
Calcium	1.6	1.0
Magnesium	1.3	1.0
Chloride	117.0	130.0
Bicarbonate	15.0	25.0
Phosphate	0.4	3.0
Lactate	7.8	-
Glucose	3.4	5.0
Ascorbate	2.0	-
Glutathione	-	0.3
Citrate	-	-
Acetate	-	-
pH	-	7.4
Osmolality (MO_sm)	-	305

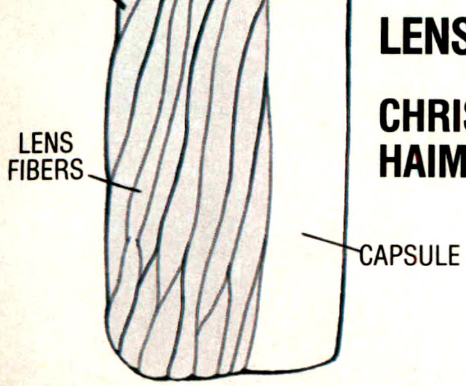
(All concentrations expressed in mmol/L)





RETINA

MOORHEAD et al (10)
WINKLER et al (11)
ALVAREZ et al (1)



LENS

CHRISTIANSEN et al (3)
HAIMANN et al (6, 7)

BSS PLUS® 30 mL and 500 mL
BRIEF SUMMARY
Based on 5/87 and 3/87 Inserts

DESCRIPTION: BSS PLUS® 30 mL is a sterile intraocular irrigating solution for use during surgical procedures requiring a relatively small volume of intraocular perfusion, e.g., anterior segment surgical procedures. The solution consists of two separate parts which are mixed aseptically prior to use. BSS PLUS® 500 mL is a sterile intraocular irrigating solution for use during intraocular surgical procedures, even those requiring a relatively long intraocular perfusion time (e.g., pars plana vitrectomy, phacoemulsification, extracapsular cataract extraction / lens aspiration, anterior segment reconstruction, etc.).

The solution does not contain a preservative and should be prepared just prior to use in surgery.

Part I: A sterile 28.8 mL solution in a 30 mL single-dose plastic bottle or a sterile 480 mL solution in a 500 mL single-dose bottle to which the Part II concentrate is added. Each mL of Part I contains: Sodium Chloride 7.44 mg, Potassium Chloride 0.395 mg, Anhydrous Dibasic Sodium Phosphate 0.433 mg, Sodium Bicarbonate 2.19 mg, Hydrochloric Acid and/or Sodium Hydroxide (to adjust pH), in Water for Injection. DM-00

Part II: 30 mL size: A sterile concentrate in a 1.2 mL single-dose syringe for addition to Part I. 500 mL size: A sterile concentrate in a 20 mL single-dose vial for addition to Part I. Each mL of Part II contains: Calcium Chloride Dihydrate 3.85 mg, Magnesium Chloride-Hexahydrate 5 mg, Dextrose 23 mg, Glutathione Disulfide (Oxidized Glutathione) 4.6 mg, in Water for Injection DM-00

After addition of BSS PLUS® Part II to the Part I bottle, each mL of reconstituted product contains: Sodium Chloride 7.14 mg, Potassium Chloride 0.38 mg, Calcium Chloride Dihydrate 0.154 mg, Magnesium Chloride Hexahydrate 0.2 mg, Anhydrous Dibasic Sodium Phosphate 0.42 mg, Sodium Bicarbonate 2.1 mg, Dextrose 0.92 mg, Glutathione Disulfide (Oxidized Glutathione) 0.184 mg, Hydrochloric Acid and/or Sodium Hydroxide (to adjust pH), in Water for Injection.

The reconstituted product has a pH of approximately 7.4. Osmolality is approximately 305 mOsm/kg.

CONTRAINDICATIONS: There are no specific contraindications to the use of BSS PLUS,® however, contraindications for the surgical procedure during which BSS PLUS® is to be used should be strictly adhered to.

WARNINGS: For IRRIGATION during ophthalmic surgery only. BSS PLUS® is NOT for injection or intravenous infusion.

PRECAUTIONS: DO NOT USE BSS PLUS® UNTIL RECONSTITUTED. Do not use Part I if it does not contain a vacuum (500 mL size). Do not use additives other than Part II. Do not use if Part I, Part II or the reconstituted solution is discolored or contains a precipitate. SINCE BSS PLUS IS INTENDED FOR INTRAOCULAR IRRIGATION, IT DOES NOT CONTAIN A PRESERVATIVE AND, THEREFORE, SHOULD NOT BE USED ON MORE THAN ONE PATIENT. DISCARD ANY UNUSED SOLUTION SIX HOURS AFTER PREPARATION. Studies suggest that intraocular irrigating solutions which are iso-osmotic with normal aqueous fluids should be used with caution in diabetic patients undergoing vitrectomy since intraoperative lens changes have been observed.

There have been reports of corneal clouding or edema following ocular surgery in which BSS PLUS® was used as an irrigating solution. As in all surgical procedures, appropriate measures should be taken to minimize trauma to the cornea and other ocular tissues.

ADVERSE REACTIONS: Rarely, postoperative inflammatory reactions as well as incidents of corneal edema and corneal decompensation have been reported. Their relationship to the use of BSS PLUS has not been established.

OVERDOSAGE: The solution has no pharmacological action and thus has no potential for overdosage. However, as with any intraocular surgical procedure, the duration of intraocular manipulation should be kept to a minimum.

U.S. Patent Nos. 4,443,432 and 4,550,022

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Glaucoma &

The Age of Risk

The fact that almost 70% of glaucoma patients are over 60 years of age[1] has important implications regarding their overall health status.

Even in younger patients, the local arteriosclerosis characteristic of glaucoma is frequently accompanied by clinical evidence of similar damage to cerebral, cardiac and renal vessels, or to the entire circulatory system.[1] The more typical older patient runs an independent risk of age-related changes in cardiopulmonary and metabolic function.

In fact, prevalence studies indicate that more than half of all glaucoma patients have concurrent cardiovascular disease,[1] and run over twice the risk of the general population of developing diabetes.[2]

DISEASE STATE	INCIDENCE COEXISTENCE WITH GLAUCOMA[1]
Hypertension	**54.5%**
Arteriosclerosis	**58.8%**
Diabetes	**15.9%**

Beyond Normotension

Such statistics mandate that your considerations in selection of a therapeutic regimen for all glaucoma patients go well beyond lowering IOP to the normotensive range.

Ophthalmic beta blockers are clearly today's drug of choice for management of elevated IOP, but the record of nonselective agents raises serious questions regarding their safety in the elderly patient. Side effects associated with orally administered nonselective beta blockers have been seen with those employed ophthalmologically.[3] In fact, all beta blockers are contraindicated in patients with sinus bradycardia, greater than a first-degree atrioventricular block, cardiogenic shock or overt cardiac failure.

Systemic effects of nonselective beta blockers[3-5]

CARDIOVASCULAR	PULMONARY
Arrhythmia	Asthma
Bradycardia	Bronchial constriction
Cerebrovascular accident	Bronchospasm
Hypotension	**DRUG INTERACTIONS**
Raynaud's phenomenon	Oral beta blockers
Syncope	Calcium antagonists
Palpitation	Reserpine
Congestive heart failure	Digitalis
	Bronchodilators
	Insulin

Systemic Spillover

The mechanisms for this "systemic spillover" of ophthalmic beta blocker effects are both pharmacologic and pharmacokinetic.

From a pharmacokinetic standpoint, it's important to note that all eyedrops drain through the nasolacrimal system rapidly. An estimated 80% of the drug may be absorbed through the nasal mucosa directly into the bloodstream, thus reaching target organs without first being metabolized in the liver (first-pass effect).[3]

Pharmacologically, nonselective agents block both beta-1 and beta-2 receptors. Thus, the potential for pulmonary and metabolic as well as cardiovascular side effects is significant.[3]

The Promise of Oculoselectivity

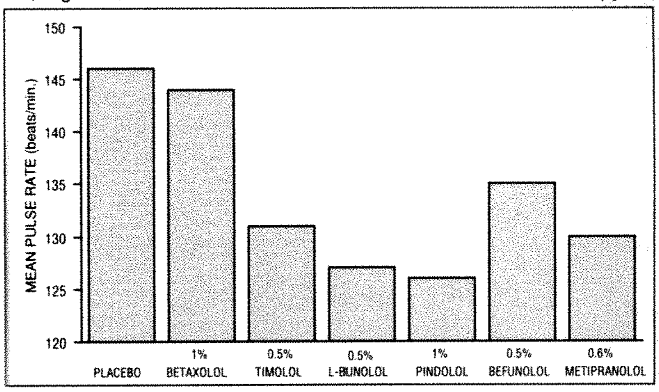
A new generation of oculoselective beta blocking agents offers hope of overcoming most of the systemic spillover associated with nonselective agents.

The beta-1 selectivity of these agents strongly diminishes their effect on organs containing beta-2 receptors and, therefore, the risk of bronchial constriction, peripheral vascular constriction and altered glucose metabolism.[4]

The pharmacokinetic profile of the oculoselective agent is similarly unique. It exhibits a high degree of lipid-solubility which permits penetration of the corneal surface in order to reach the desired site of action.[6]

Lipid-solubility, furthermore, accounts for a high volume of distribution throughout extra- and intracellular spaces, so that beta-blocking activity remains low throughout the body. In addition, more drug is bound to plasma protein, and less free drug is available to interact with receptors throughout the body. Such is not the case with nonselective beta blockers which exhibit significant plasma activity even after ophthalmic administration.[6]

Numerous clinical studies support the lack of systemic spillover with oculoselective beta blockers. These agents demonstrate little effect on cardiopulmonary function, and would not be expected to interfere with concomitant medications including calcium channel blockers, diuretics, digitalis, oral beta blockers, bronchodilators or insulin therapy.[7-10]



Relative effects of selective and various nonselective beta-blocking agents on pulse rate of 6 normal subjects following 10 minutes of exercise.[11]

Clearly, the choice of an oculoselective beta blocker addresses concerns that go well beyond achievement of normotension for the typical glaucoma patient in "the age of risk."

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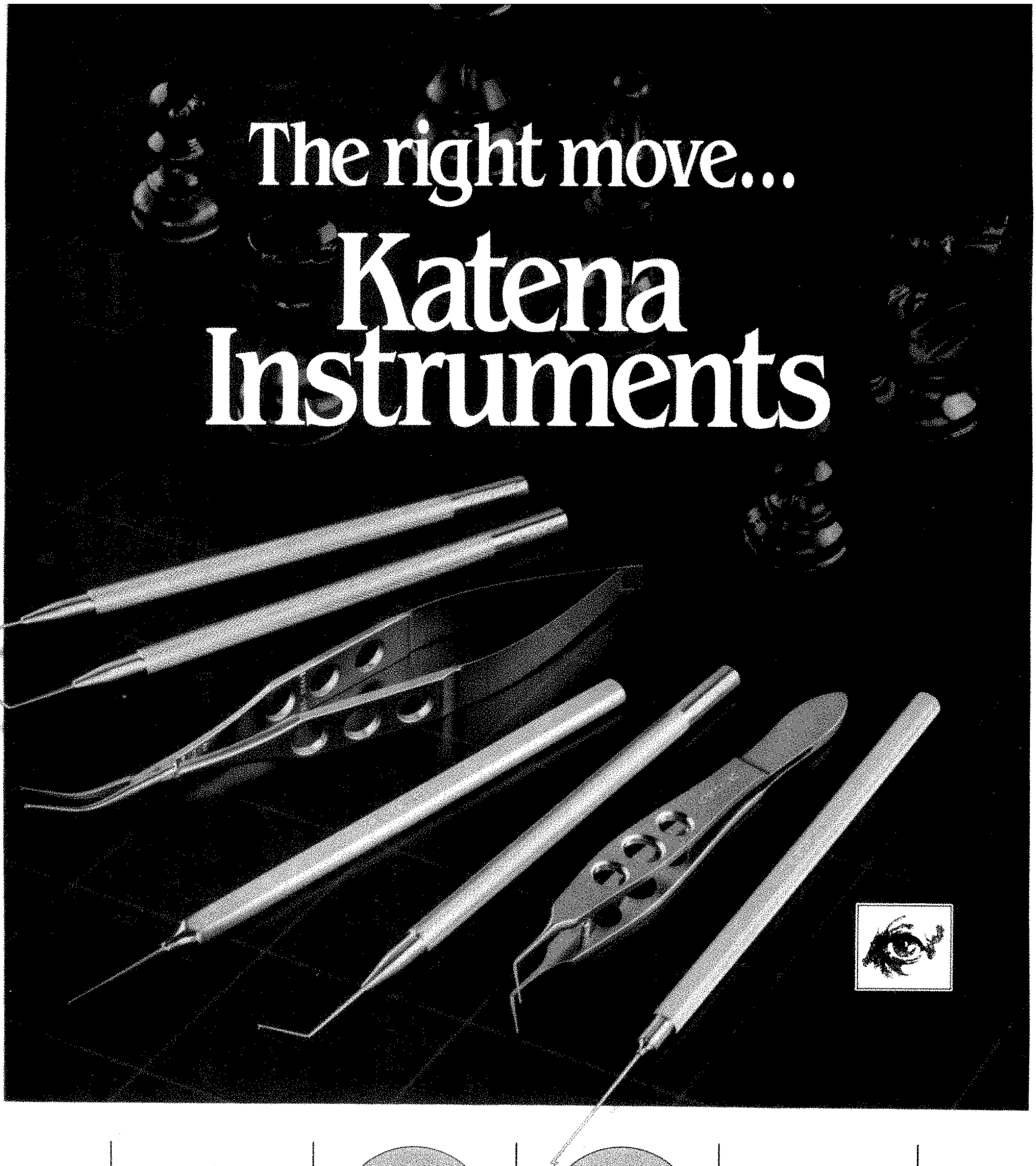

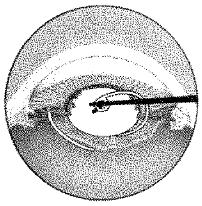

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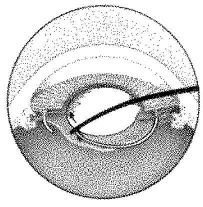
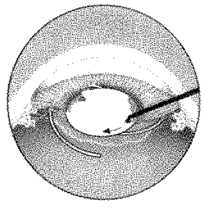
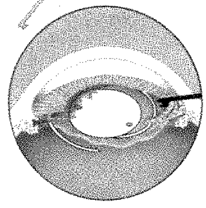
V-shaped tip for positioning superior loop with hole in distal end.
K3-5532 str.
K3-5533 ang.



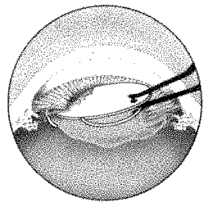
Lester Lens Pusher
Hourglass shaped tip is suitable for manipulating lenses with and without holes. Shaft is vaulted to reach the inferior loop without pressing on the optic.
K3-2691



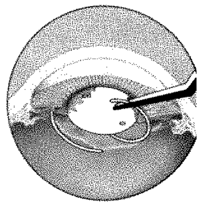
Sinskey Lens Hook
For manipulating IOL's with holes. Available with flat or round handle.
K3-5220 flat, str.
K3-5230 flat, ang.
K3-5232 round, str.
K3-5233 round, ang.



Kuglen Iris Hook
Used as an iris retractor, lens guide or lens manipulator. Available with round or flat handle.
K3-5500 flat, str.
K3-5520 flat, ang.
K3-5522 round, str.
K3-5523 round, ang.



Knolle-Volker Lens Holding Forceps
Peg in upper jaw fits hole in optic while notch in lower jaw holds superior loop for simultaneous insertion of optic and loop.
K5-8461



Kelman-McPherson Forceps, *7.5mm thin jaws*. The most frequently used instrument for IOL insertio May be used for grasping optic or loo
K5-5030

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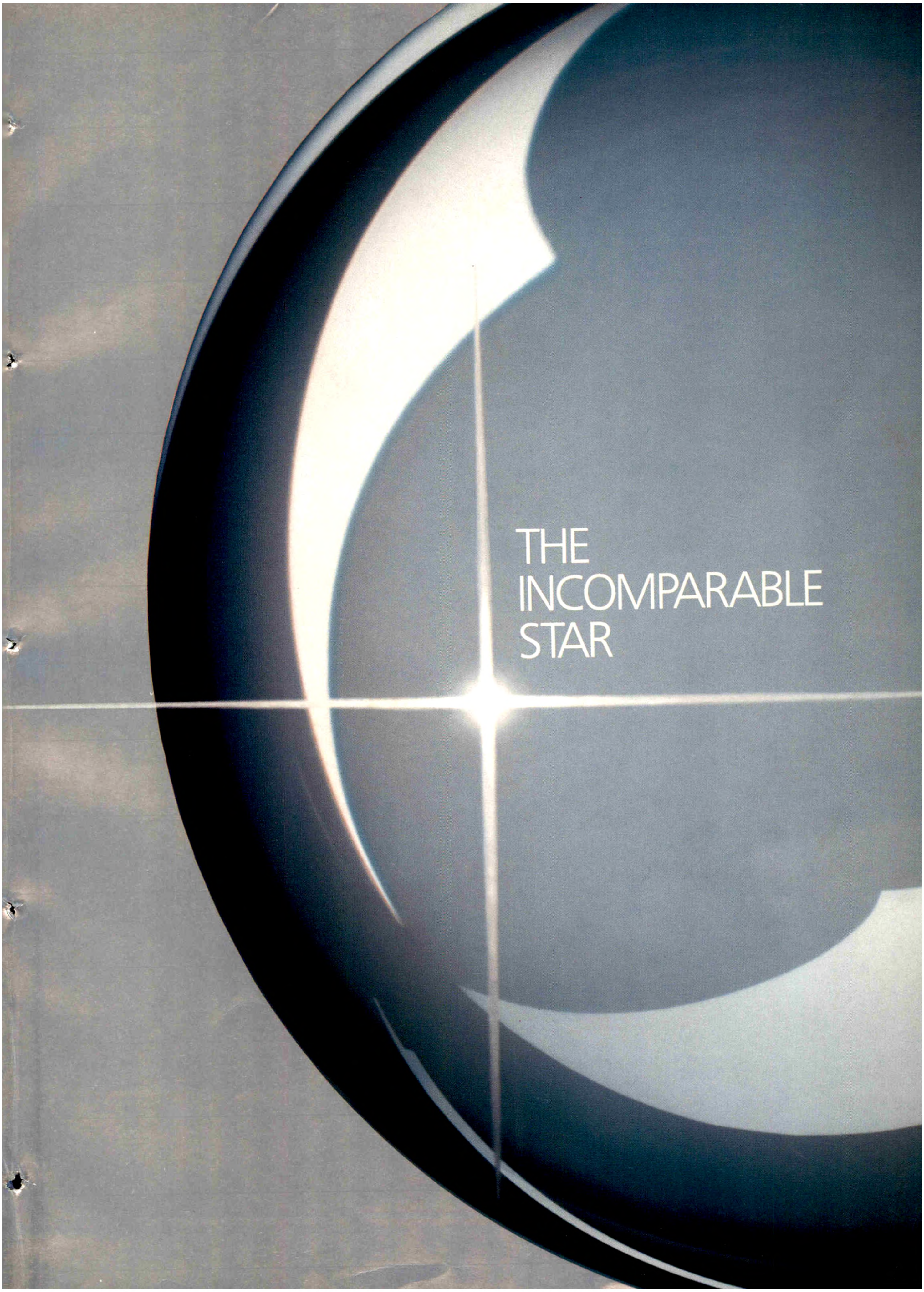
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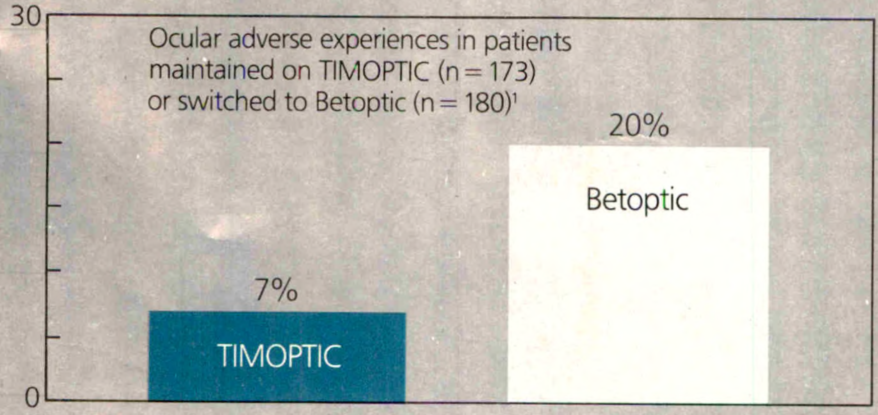

Many patients who were switched from therapy with TIMOPTIC to Betoptic experienced an increase in ocular discomfort.

Treatment with TIMOPTIC caused significantly fewer incidences of burning, stinging, and tearing than with Betoptic.

*In a multicenter, double-masked, randomized, parallel study, 353 patients with a history of satisfactory IOP control and tolerability while on TIMOPTIC were treated for 12 weeks with either TIMOPTIC 0.5% b.i.d. or Betoptic 0.5% b.i.d. ($p \leq 0.01$).

[1]Data available upon request from Merck Sharp & Dohme, Professional Information, West Point, PA 19486-9989.

Five patients had a serious adverse experience during the study: four in the timolol treatment group and one in the betaxolol treatment group. Investigators considered four of these incidences either "definitely" not drug related or "probably" not drug related. One incident was considered "possibly" drug related; however, the patient continued in the study until relative Day 43.

Five patients were discontinued from the timolol treatment group due to an adverse experience. Ten patients were discontinued from the betaxolol treatment group due to an adverse experience.

Patients who are receiving a beta-adrenergic blocking agent orally and TIMOPTIC should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

TIMOPTIC is contraindicated in patients with bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease (see WARNINGS); sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; and hypersensitivity to any component of this product.

NOTE: Betoptic is the registered trademark of Alcon Laboratories, Inc. for betaxolol hydrochloride.

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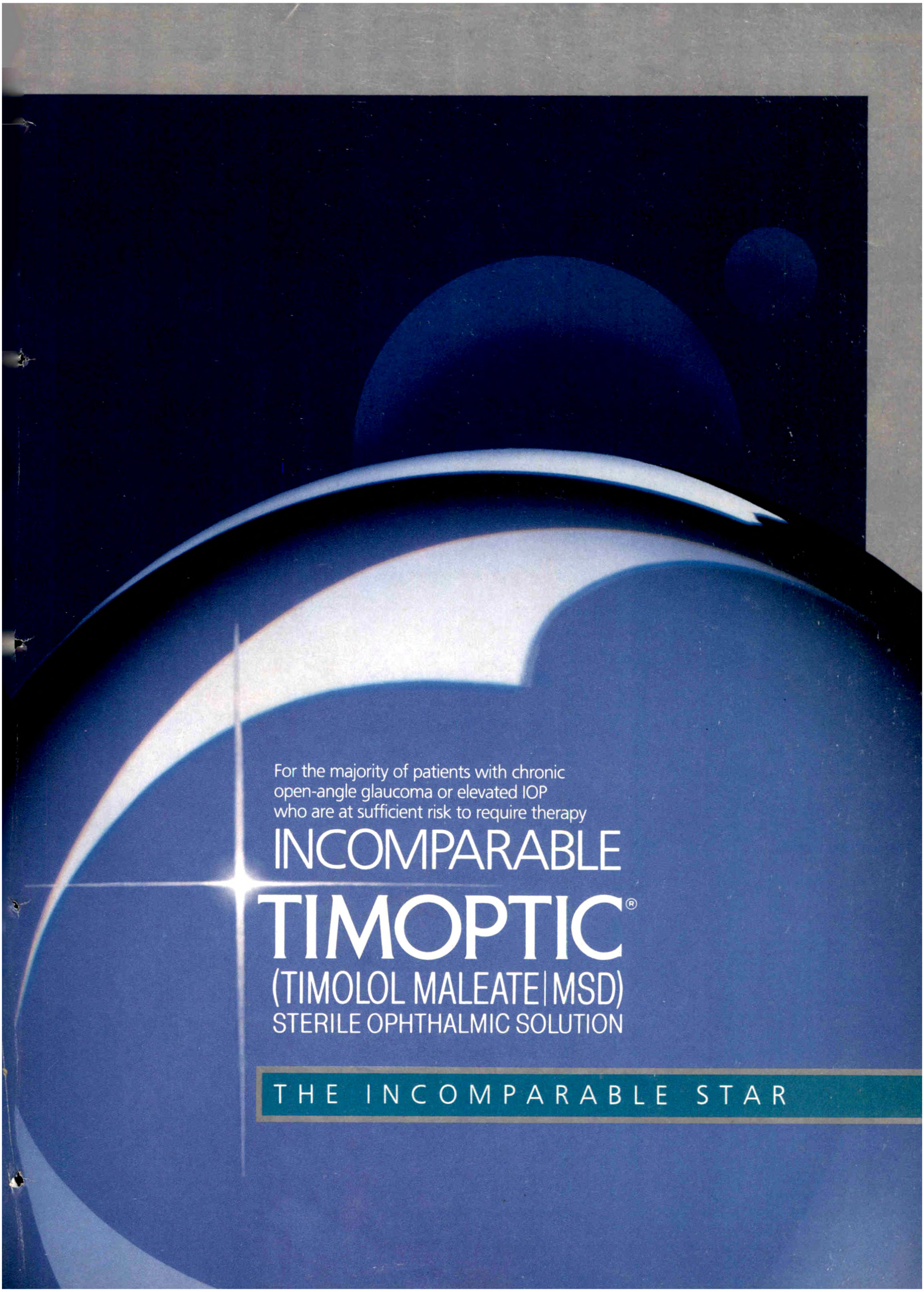
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Trabecular Repopulation by Anterior Trabecular Meshwork Cells After Laser Trabeculoplasty

Ted S. Acott, Ph.D., John R. Samples, M.D., John M. B. Bradley, B.S., David R. Bacon, B.S., Stephen S. Bylsma, B.S., and E. Michael Van Buskirk, M.D.

To study further the transient increase in trabecular cell division within the first two days after laser trabeculoplasty in human corneoscleral explant organ cultures, we used a pulse-chase protocol in which immediately after laser treatment ^{3}H-thymidine was added to the culture medium for 48 hours (the pulse period). Fresh medium without radiolabel was then added for variable times (the chase period) before termination of the experiment. Autoradiography was used to follow changes in the regional distribution of the cells that divided during the pulse period and had ^{3}H-thymidine-labeled DNA. Laser-treated explants, evaluated after a pulse with no chase, showed a fourfold increase in cell division ($P < .001$) over nontreated controls. Nearly 60% of this cell division was localized to the anterior, nonfiltering region of the trabecular meshwork where it inserts into the cornea beneath Schwalbe's line. Trabecular cell division in other regions of the meshwork was not increased over controls at this time.

After seven or 14 days of chase without radiolabel, the regional distribution of radiolabeled cells changed in laser-treated explants but not in controls. By 14 days, only 26% of the labeled cells remained in this anterior insert region, while 60% were found in the region of the burn sites. Macroautoradiography of whole explants corroborated these observations. Our data support the hypothesis that laser trabeculoplasty causes early cell division by a population of cells in the anterior meshwork; these new cells then migrate and repopulate the burn sites over the next few weeks.

© American Journal of Ophthalmology 107:1–6, January, 1989

Effects of Carbachol and Acetylcholine on Intraocular Pressure After Cataract Extraction

Richard S. Ruiz, M.D., Marcus N. Rhem, and Thomas C. Prager, Ph.D.

We compared the effect of carbachol and acetylcholine on intraocular pressure 24 hours after extracapsular cataract extraction. All agents were administered intracamerally at the time of surgery. Sixty patients scheduled for routine extracapsular cataract extraction and intraocular lens implantation were randomly assigned into one of three treatment groups: (1) carbachol, (2) acetylcholine, or (3) 0.5% balanced salt solution (placebo). Baseline intraocular pressures were determined the day before surgery, and postoperative pressures were measured approximately 24 hours after surgery. The group intraocular pressures averaged over preoperative and postoperative values were 21.06 mm Hg in the acetylcholine group, 19.36 mm Hg in the control group, and 17.30 mm Hg in the carbachol group. The average difference between preoperative and postoperative intraocular pressure measurements for the three groups were 7.33 mm Hg for the acetylcholine group, 8.73 mm Hg for the control group, and 2.20 mm Hg for the carbachol group. Only carbachol was significantly different from placebo on statistical subsequent testing. Carbachol is suggested as the agent of choice both for achieving intrasurgical miosis and prophylaxis of increasing intraocular pressure after cataract surgery.

© American Journal of Ophthalmology 107:7–10, January, 1989

Intraocular Pressure Effects of Carbonic Anhydrase Inhibitors in Primary Open-Angle Glaucoma

Paul R. Lichter, M.D., David C. Musch, Ph.D., Fedor Medzihradsky, Ph.D., and Carol L. Standardi, R.N.

We tested the effect on intraocular pressure of three commonly used oral carbonic anhydrase inhibitor preparations in a controlled, randomized, comparative study on patients with primary open-angle glaucoma. Preparations tested included acetazolamide tablets, acetazolamide Sequels, and methazolamide tablets. The effect of the three carbonic anhydrase inhibitors was assessed by using a statistical modeling approach as well as by evaluating the average maximum reduction in intraocular pressure for each preparation. Dosage and time effects were also determined. As expected, each drug preparation was more effective in reducing intraocular pressure when administered to a patient who had already been treated with the carbonic anhydrase inhibitor preparation. The amount of intraocular pressure lowering was directly related to dose for both acetazolamide preparations. Of particular interest was the finding that maximal rapid reduction of intraocular pressure was obtained with a 500-mg dosage of acetazolamide tablets.

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Intraocular Pressure After Cardiopulmonary Bypass Surgery

David Deutch, M.D., and Richard A. Lewis, M.D.

The ocular effects of cardiopulmonary bypass surgery were prospectively studied in 46 patients. We examined preoperative and postoperative visual acuity, intraocular pressure, body weight, fluids infused during surgery, hematocrit, and cardiopulmonary bypass time. On the first postoperative day mean intraocular pressure increased 2.1 mm Hg ($P = .003$) from baseline preoperative levels. Over the first postoperative day intraocular pressure increased in 29 (63%) of the patients. Three patients (7%) had a greater than 10 mm Hg rise. The mean intraocular pressure returned to baseline by the third postoperative day. Patient weight increased from preoperative levels an average of 9.3 lbs ($P < .0001$) on day 1 and 6.5 lbs on day 3. Mean hematocrit decreased 11.3% ($P < .0001$) on day 1 from baseline and remained at that level through day 3. None of the patients complained of visual dysfunction during the course of this study and none showed more than a two-line decrease in near visual acuity. The increase in intraocular pressure did not correlate with the postoperative weight gain or hemodilution. However, the medications necessary after cardiac surgery may be a significant confounding variable. This study demonstrates that one cause of ocular problems from cardiopulmonary bypass surgery may be related to the dynamics of intraocular pressure.

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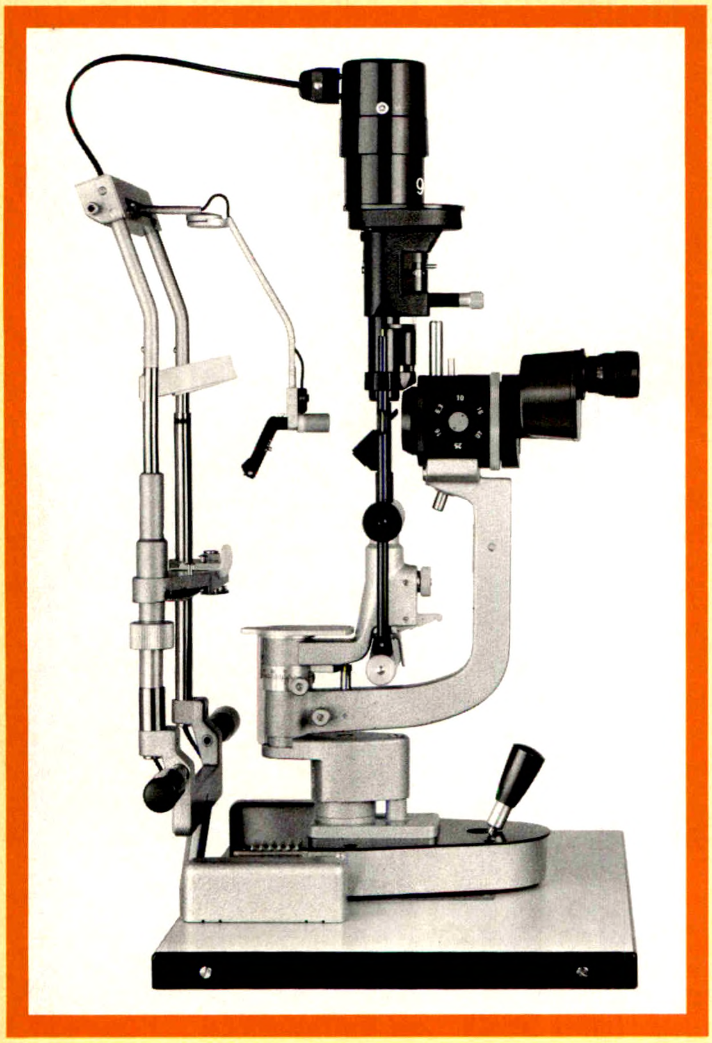

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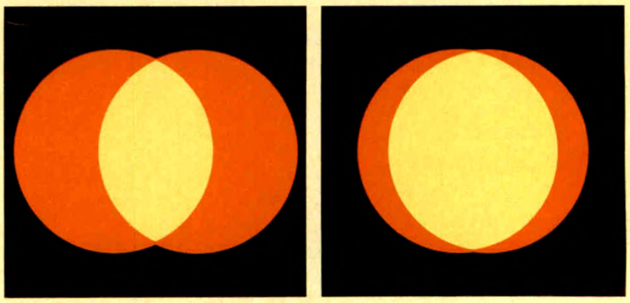

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Intractable Diplopia After Vision Restoration in Unilateral Cataract

John A. Pratt-Johnson, F.R.C.S.(C.), and Geraldine Tillson, D.B.O.(T.)

Twenty-four patients lost their ability to fuse when their binocular function was disrupted for at least 2½ years by a unilateral traumatic cataract or a unilateral traumatic cataract followed by uncorrected aphakia. Three patients were 6 years old, one was 8 years old, and the remaining 20 patients were aged 10 years or older at the time of the injury. All patients had intractable diplopia when the cataract was removed and the aphakia corrected. Aniseikonia was not the cause of this inability to fuse and the insertion of an intraocular lens provided no relief. The prognosis for the elimination of diplopia, other than by occlusion of one eye, was poor.

© American Journal of Ophthalmology 107:23–26, January, 1989

Contact Lens-Related Deep Stromal Neovascularization

Yaacov Rozenman, M.D., Eric D. Donnenfeld, M.D., Elisabeth J. Cohen, M.D., Juan J. Arentsen, M.D., Vitaliano Bernardino, Jr., M.D., and Peter R. Laibson, M.D.

We observed five eyes (five patients) with deep stromal neovascularization and scarring in patients wearing soft contact lenses during a six-month period. There was no evidence suggestive of other causes of interstitial keratitis. Two patients were aphakic and required a penetrating keratoplasty. Deep stromal vascularization must be added to the growing list of visually significant soft contact lens complications, and soft lens wear should be considered in the differential diagnosis of deep stromal neovascularization.

© American Journal of Ophthalmology 107:27–32, January, 1989

Nd:YAG Laser Photodisruption of Hemorrhagic Detachment of the Internal Limiting Membrane

V.-P. Gabel, M.D., Reginald Birngruber, Ph.D., H. Gunther-Koszka, M.D., and Carmen A. Puliafito, M.D.

We used a Q-switched Nd:YAG laser to create an opening in the internal limiting membrane in three eyes with hemorrhagic detachment of the internal limiting membrane. In all instances, after membranotomy blood was rapidly cleared from the preretinal space resulting in prompt improvement in visual acuity. No retinal injury was observed. Nd:YAG laser photodisruption may be useful in the treatment of some cases of subinternal limiting hemorrhages.

© American Journal of Ophthalmology 107:33–37, January, 1989

Subretinal Hemorrhage in Atrophic Age-Related Macular Degeneration

Fadi Nasrallah, M.D., Alex E. Jalkh, M.D., Clement L. Trempe, M.D., J. Wallace McMeel, M.D., and Charles L. Schepens, M.D.

In eight eyes of eight patients we retrospectively studied the outcome of subretinal hemorrhage occurring in areas of atrophy of retinal pigment epithelium and choriocapillaris secondary to age-related macular degeneration. These patients were followed up for one to 20 months after the initial appearance of the hemorrhage. No subretinal new vessels were associated with these hemorrhages, which resolved over one to l5 months. Our findings indicated that hemorrhages occurring within areas of atrophy are not necessarily associated with subretinal new vessels, and that this type of hemorrhage has a good prognosis for resolution.

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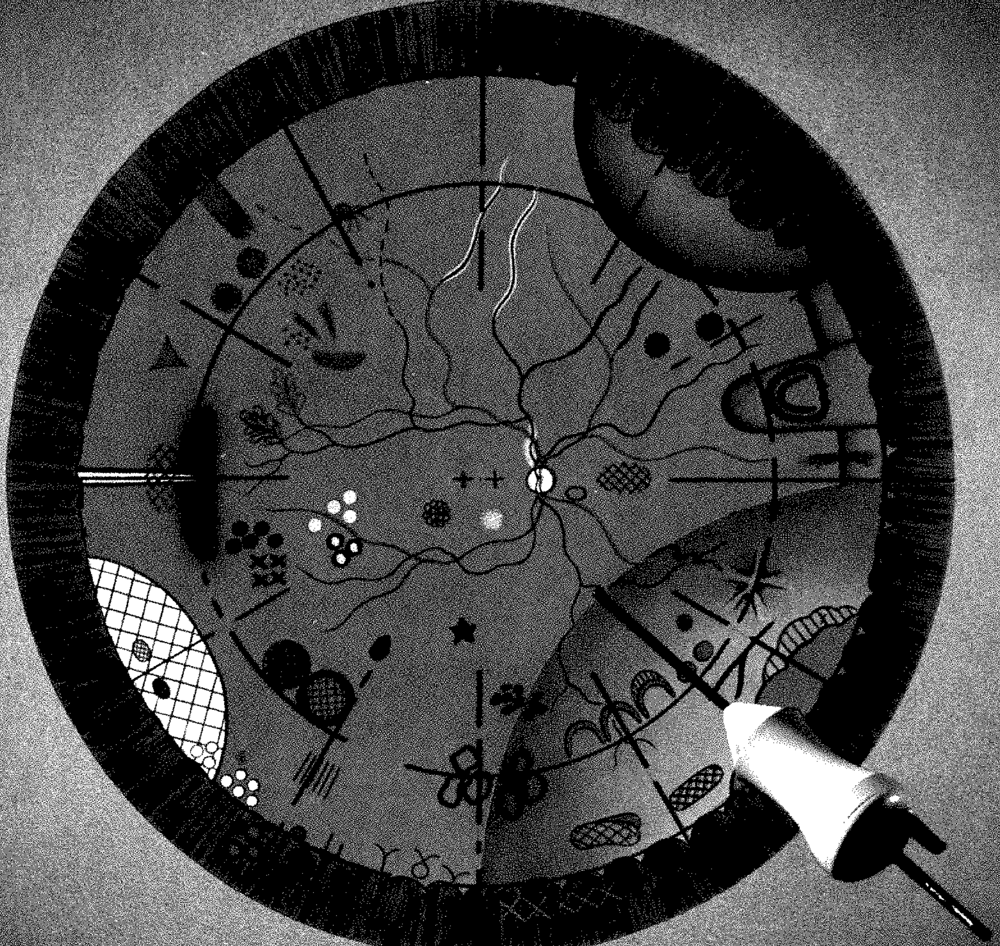

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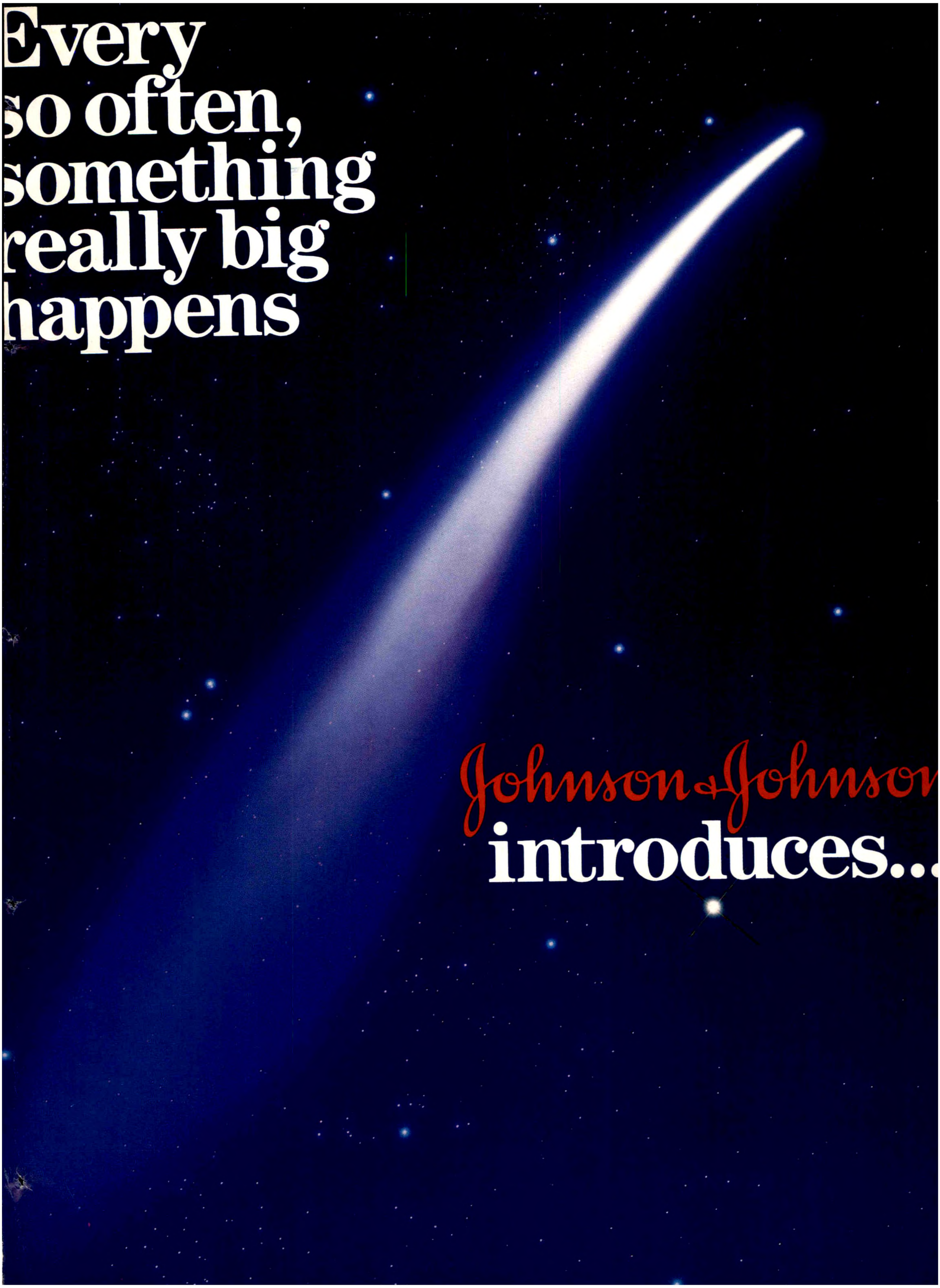

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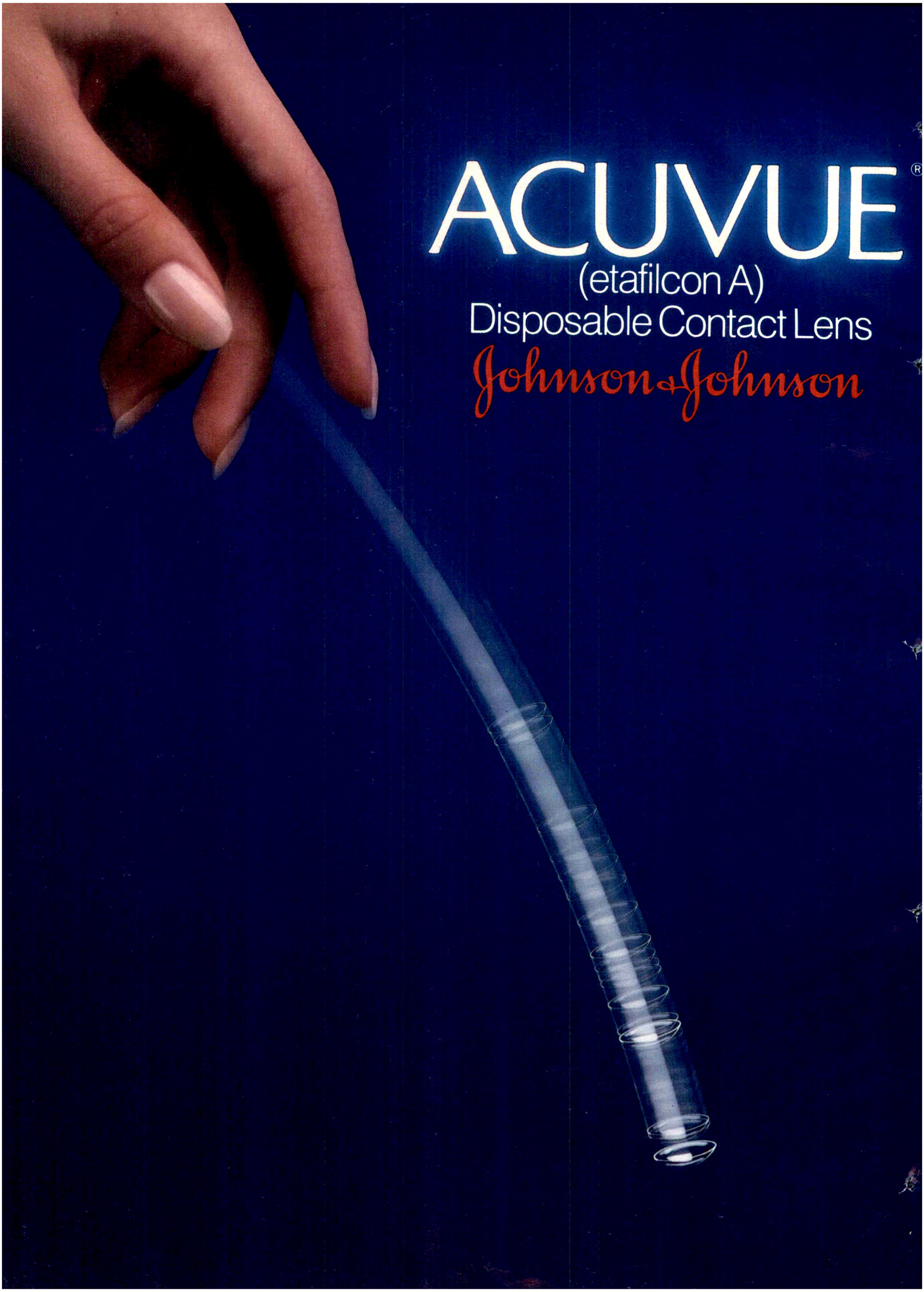
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The first truly disposable contact lens

Now available! The disposable lens that never needs cleaning

Now…a significant advance in contact lens wear: patients wear ACUVUE lenses for about 1 week, then simply dispose of and replace them with a new, sterile pair! No cleaning or disinfecting is needed because the lens is used only once.

Breakthrough technology makes it possible

Years of research and development have made possible the production of ACUVUE lenses by a unique new *Stabilized Soft Molding* process, whereby ACUVUE is produced entirely in the soft, wet state. This multipatented process provides an entirely new standard of precision, eliminating the hydration distortions common to traditional hard state manufacturing. The result is a totally new, high quality lens that is virtually 100% repeatable, offering excellent vision and comfort, and making disposability a practical reality.

Superior visual acuity

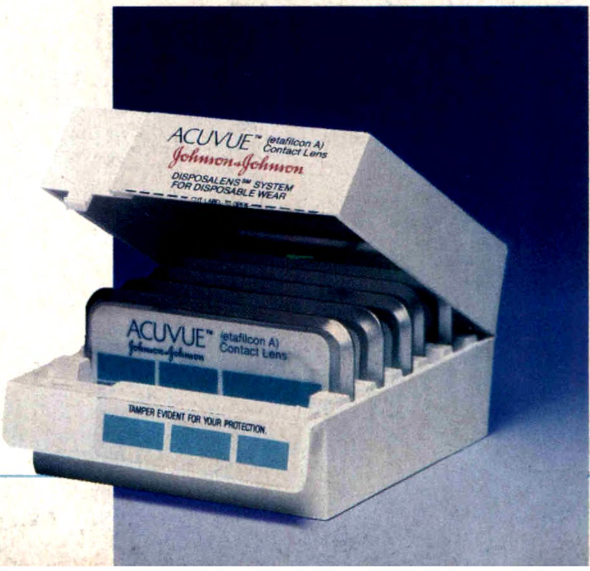
When eye care practitioners compared ACUVUE to conventional, reusable contact lenses, 71% rated ACUVUE superior in visual acuity.[1] And 69% of patients surveyed agreed that ACUVUE provided crisper, sharper vision than their previous form of vision correction.[2]

Superior comfort

In a recent survey of practitioners, 85% agreed that their patients reported comfort as better or superior to conventional, reusable contact lenses.[1] Patient response was especially favorable: no less than 77% reported ACUVUE to be more comfortable week after week.[2]

Most importantly, ACUVUE provides this outstanding performance in visual acuity, comfort, and reliability continually, lens after lens after lens!

Now the better choice in vision correction is here!



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Scanning electron photo-micrographs demonstrate the ACUVUE advantage:

An extended wear lens after 1 month with patient care: Deposit buildup evident*

A daily wear lens after 1 month with patient care: Deposit buildup evident*

ACUVUE Disposable Contact Lens after 1 week: Minimal deposit buildup

And since cleaning and disinfecting solutions are eliminated with the disposable regimen, patients using ACUVUE are not at risk for allergic reactions associated with solutions. Here's what practitioners reported when asked about the ACUVUE health advantage: 95% agreed that disposable wear was safer and healthier than conventional, reusable contact lenses![1]

The most convenient regimen for patient compliance

ACUVUE makes patient compliance as simple as possible: patients simply dispose of the lenses after use. That means there is no care regimen for them to follow. No solutions to buy, use, or carry. No time expended for maintenance. No inconvenience. Nothing could be simpler than the ACUVUE easy-to-follow wear schedule. In fact, 98% of practitioners surveyed found that patient compliance with ACUVUE met or exceeded their expectations!

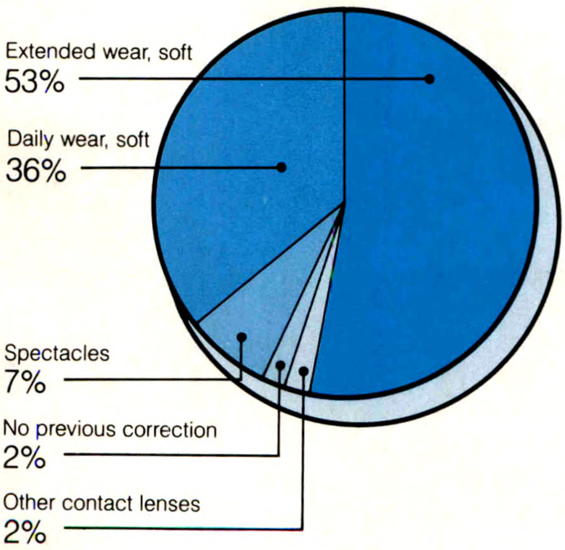
*Representative of over 50 lenses obtained by an independent practitioner from patients who reported their compliance regimens.

Now the better choice in vision correction is here!

An outstanding practice building opportunity for you

Here's what ACUVUE can provide specifically for your practice: increased profits per patient; greater patient retention because you control the supply of lenses; ongoing revenue, plus the potential to substantially increase your patient base...including the possibility of recapturing contact lens dropouts.

Source of ACUVUE Patients



Test markets in Florida and California demonstrated that patient interest and acceptance exceeded all forecasts for ACUVUE. In fact, a very broad base of patients, not just current contact lens wearers, readily switched to ACUVUE.

Satisfaction was outstanding: 94% of patients using ACUVUE lenses stated they were satisfied and would continue with them.[2] What's more, 98% would refer others to try ACUVUE![2]

To draw even more patients to your practice, Johnson & Johnson is planning a significant consumer advertising and promotion campaign which will create substantial demand for ACUVUE on a national level.

ACUVUE combines the convenience patients want from a contact lens, with the many benefits you want for them. It all adds up to a unique new practice building opportunity.

ACUVUE: The first truly disposable contact lens... the better choice in vision correction!

References: 1. Comparison of ACUVUE lenses to soft spherical contact lenses. Practitioner Survey, data on file, VISTAKON, INC. 2. Patient use survey, data on file, VISTAKON, INC.

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Irregular Astigmatism After Radial and Astigmatic Keratotomy

Peter J. McDonnell, M.D., Patrick J. Caroline, B.A., and James Salz, M.D.

Eleven eyes of six patients, who had been referred for management of irregular astigmatism after receiving crossed incisions for myopic astigmatism, had moderate to marked irregular corneal astigmatism with marked flattening in the meridians of intersecting incisions. All six patients had a decrease in best-corrected visual acuity with spectacles after surgery. Visual acuity with spectacles was 20/40 in five of 11 eyes; with contact lenses it reached 20/40 in ten of 11 eyes. However, two patients could not wear the contact lenses because of lens decentration caused by the marked distortion in corneal topography. Even with contact lenses, visual acuity could only be improved to 20/25 or better in six of 11 eyes.

© American Journal of Ophthalmology 107:42–46, January, 1989

Excimer Laser-Processed Donor Corneal Lenticules for Lamellar Keratoplasty

Shimon Gabay, Ph.D., Allan Slomovic, M.D., and Tony Jares, Ing.C.

We used the 193-nm argon-fluoride excimer laser to cut plano corneal lenticules from fresh corneal tissue for lamellar keratoplasty. The laser was used to cut away all corneal tissue outside a specially designed mold, which was developed to obtain a corneal lenticule of 10 mm in diameter and a constant thickness of 0.3 mm. The surface topography of the excimer laser-cut corneal lenticule was smoother and more regular on scanning electron microscopy than a hand-cut corneal lenticule, and the thickness was constant around the surface. No thermal or mechanical damage to the cornea was observed on light microscopy in the area adjacent to the cut.

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Edema of the Corneal Stroma Induced by Cold in Trigeminal Neuropathy

Steven E. Wilson, M.D., James A. Garrity, M.D., and William M. Bourne, M.D.

A patient with a left sensorimotor trigeminal neuropathy was found to have edema of the corneal stroma induced by cold. Examination at room temperature demonstrated an anesthetic left cornea with minimal injection of the left eye and multiple punctate epithelial erosions. Corneal thickness, mean endothelial cell size, coefficient of variation of cell size, endothelial permeability to fluorescein, and aqueous humor flow rate as measured at room temperature were similar in the two eyes. After 47 minutes in a cold room at 4 C, the corneal thickness in the left eye increased from 0.55 to 0.65 mm, whereas that of the right eye remained at 0.55 mm. During the period of maximum swelling, the left cornea had clinical stromal edema with folds in Descemet's membrane but no epithelial edema. After return to room temperature there was a gradual return to normal corneal thickness over three hours. Fluorophotometry showed no evidence of increased endothelial permeability during corneal swelling in the left eye. Specular microscopy after 15 minutes of cold exposure demonstrated many swollen and irregular endothelial cells with darkened areas between cells in the left eye. Sensory nerve deficiency in the human cornea can produce an abnormal sensitivity to cold, resulting in defective control of corneal hydration. This study suggests that this effect may be on the endothelium.

© American Journal of Ophthalmology 107:52–59, January, 1989

Rapid Streptococcal Antigen Detection in Experimental Keratitis

Warren M. Sobol, M.D., Jaime Torres Gomez, M.D., Michael S. Osato, Ph.D., and Kirk R. Wilhelmus, M.D.

We assessed the role of commercially available immunodiagnostic procedures in comparison to Gram stain and culture in experimental bacterial keratitis. Rabbit corneas were inoculated with *Streptococcus pneumoniae, S. pyogenes, S. faecalis,* or *Haemophilus influenzae*. Corneal scrapings were processed before and during antibacterial therapy using a coagglutination assay to detect pneumococcal capsular antigen (Phadebact Pneumococcus test) and an enzyme immunoassay to detect group A streptococcal cell-wall antigen (TestPack Strep A test). In untreated infected eyes, both immunoassays were highly specific and as sensitive as Gram stain for detection of the respective microorganisms. For *S. pneumoniae* keratitis, the sensitivity of coagglutination was 82% and Gram stain, 73%. For *S. pyogenes* keratitis, the sensitivity of enzyme immunoassay was 100% and Gram stain, 62%. Immunoassays and Gram stain were less sensitive than culture during antibacterial therapy. Successful clinical application of the coagglutination assay in a patient with pneumococcal keratitis permitted early use of specific cephalosporin treatment.

© American Journal of Ophthalmology 107:60–64, January, 1989

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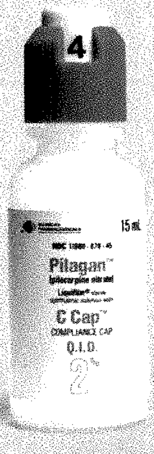

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VOLUME 107 NUMBER 1 JANUARY, 1989

Trabecular Repopulation by Anterior Trabecular Meshwork Cells After Laser Trabeculoplasty

Ted S. Acott, Ph.D., John R. Samples, M.D., John M. B. Bradley, B.S., David R. Bacon, B.S., Stephen S. Bylsma, B.S., and E. Michael Van Buskirk, M.D.

To study further the transient increase in trabecular cell division within the first two days after laser trabeculoplasty in human corneoscleral explant organ cultures, we used a pulse-chase protocol in which immediately after laser treatment ^{3}H-thymidine was added to the culture medium for 48 hours (the pulse period). Fresh medium without radiolabel was then added for variable times (the chase period) before termination of the experiment. Autoradiography was used to follow changes in the regional distribution of the cells that divided during the pulse period and had ^{3}H-thymidine-labeled DNA. Laser-treated explants, evaluated after a pulse with no chase, showed a fourfold increase in cell division ($P < .001$) over nontreated controls. Nearly 60% of this cell division was localized to the anterior, nonfiltering region of the trabecular meshwork where it inserts into the cornea beneath Schwalbe's line. Trabecular cell division in other regions of the meshwork was not increased over controls at this time.

After seven or 14 days of chase without radiolabel, the regional distribution of radiolabeled cells changed in laser-treated explants but not in controls. By 14 days, only 26% of the labeled cells remained in this anterior insert region, while 60% were found in the region of the burn sites. Macroautoradiography of whole explants corroborated these observations. Our data support the hypothesis that laser trabeculoplasty causes early cell division by a population of cells in the anterior meshwork; these new cells then migrate and repopulate the burn sites over the next few weeks.

Accepted for publication Oct. 13, 1988.

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LASER TRABECULOPLASTY is beneficial for certain patients with open-angle glaucoma[1]; however, our limited understanding of the mechanism of action of this treatment restricts our ability to refine the procedure. To account for the decrease in intraocular pressure that follows laser trabeculoplasty, both mechanical tension[2,3] and active cellular mechanisms[4-7] have been postulated. Changes that have been observed in the meshwork after laser treatment include different vacuolization patterns at Schlemm's canal,[4,8] cellular proliferation and overgrowth,[7-9] alterations in the trabecular glycosaminoglycan profiles,[6] an initial decrease in trabecular cell density followed by repopulation,[6] and modulations of the rate of trabecular cell division.[10]

The relationship between the response to laser trabeculoplasty as depicted by these biologic activities and the clinical efficacy of this treatment has not been established. An observed increase in the level of trabecular cell division during the first two days after treatment,[10] at a time when cell density in the laser-burn sites is low,[6] prompted us to hypothesize that cell replication may account for at least a portion of the observed repopulation of laser burn sites with time.[6] To begin testing this hypothesis, we used a pulse-chase protocol in which the pulse (addition of radioactive thymidine to the medium for 48 hours immediately

after laser treatment) resulted in the incorporation of radioactive thymidine into the DNA of replicating cells, and the chase (zero, seven, or 14 days in culture in medium without radioactivity) allowed us to track the radiolabeled cells that had divided during the first 48 hours after laser treatment.

Material and Methods

Human eye bank eyes, obtained from the Lion's Eye Bank of Portland, Oregon within 48 hours of death, were placed in corneoscleral explant organ culture.[11] Use of human tissue was in compliance with the requirements of the Public Health Service and protocols were reviewed and approved by Oregon Health Sciences University's Institutional Review Board on Human Subjects. Culture and laser treatment conditions have been presented in detail.[10,11] Briefly, human explants were cultured for seven days in serum-free medium (changed every two or three days), placed in sterile sealed-glass chambers, and subjected to laser trabeculoplasty (50 uniformly spaced burns over 180 degrees of meshwork of the explant) using an argon-dye laser at 1.0 W for 0.1 second with a focused 50-μm spot size directed slightly anterior to the center of the filtering portion of the trabecular meshwork. Untreated paired donor controls were treated similarly but did not actually receive the laser burns. Radiolabeling (the pulse) was for 48 hours with 3 μCi/ml ^{3}H-thymidine or 10 μCi/ml ^{14}C-thymidine, respectively added to the medium immediately after laser or control treatment. For chases (zero, seven, and 14 days), explants were washed three times and then cultured in fresh medium without radiolabel for the times indicated. Fixation, sectioning, and autoradiography have been described previously.[10] Explants were rinsed in fresh medium, bisected, fixed for 24 to 48 hours at 4 C in 2.5% glutaraldehyde in 0.1 M cacodylate buffer, pH 7.4, and dehydrated through a graded alcohol series. Tissue blocks were infiltrated with and embedded in glycol methacrylate, 3-μm sections were cut with glass knives, dried on glass slides, and dipped in a 1:1 water dilution of photographic emulsion. After exposure for 48 hours at 4 C, the photographic emulsion was developed and fixed. The slides were then stained with 0.1% toluidine blue in 0.1% sodium borate, destained in dilute hydrochloric acid, rinsed, and analyzed.

Meridional sections through random, nonadjacent regions of all quadrants of each explant were placed with 16 sections on each slide and the code was masked before the slide was processed and analyzed. Each step (sectioning, counting, and data analysis) was conducted by a different investigator. Three or more explants were analyzed from each group. A labeled cell was defined as one with more than 20 distinct grains in the autoradiographic emulsion over the nuclei; grains and pigment granules were differentiated by changing focal planes using oil emersion and a 100× objective. The number of labeled and unlabeled nuclei were counted (using 100× and 25× objectives, respectively) for each total meshwork and for each anterior meshwork insert region. The position of each labeled nucleus was also marked on a diagram for detailed regional analysis. For this analysis, the meshwork was divided into four observation regions: the anterior region where the trabecular meshwork inserts into the cornea beneath Schwalbe's line, the laser-treatment burn region, the region near Schlemm's canal, and the remainder of the meshwork or posterior region. Student's *t*-test was used to determine the statistical significance of differences between groups.

Results

Autoradiographs of the anterior insert region of the meshwork after a zero-day chase and of a laser burn site after a 14-day chase in culture (Fig. 1) showed typical radiolabeling patterns. When the microscope was focused either on the cells or on the emulsion grains, which are found in separate planes of focus, labeled nuclei were easily apparent. We found a relatively dense packing of the cells and extracellular matrix in the anterior insert region of the meshwork (Fig. 2). This area is discrete and the cellular population is easily differentiated from the corneal endothelium and from the corneal stroma. This triangular insert broadens and becomes open or "filtering" meshwork at the anterior edge of Schlemm's canal. In the burn region, although a considerable amount of tissue repair and cellular repopulation had occurred by 14 days, the trabecular corneoscleral sheets and uveal cords were still not completely

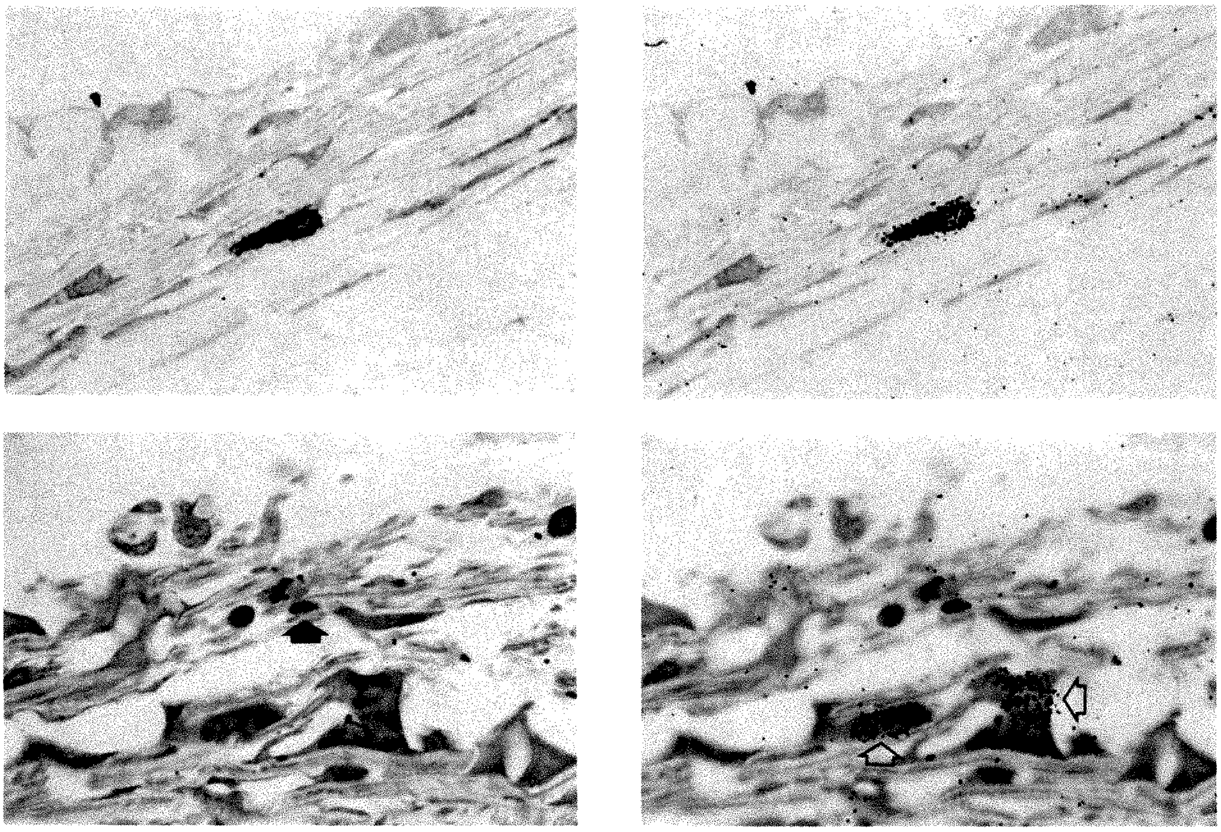

Fig. 1 (Acott and associates). Photomicrographs of typical laser-treated trabecular autoradiographs. Anterior insert region of a zero-day chased meshwork focusing on cells (top left) and on emulsion grains (top right). Burn site region of a 14-day chased meshwork focusing on cells (bottom left) and on emulsion grains (bottom right). The solid arrow marks pigment granules while the two open arrows mark labeled nuclei. Photomicrographs were taken with a 100× objective and oil immersion.

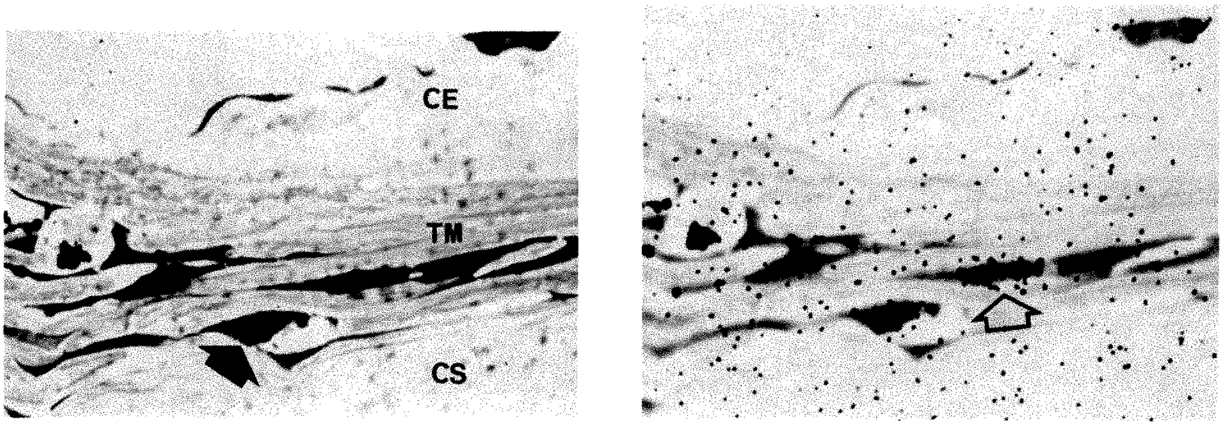

Fig. 2 (Acott and associates). Photomicrographs of the anterior insert region showing the discrete nature of this region. The solid arrow (left) indicates typical pigment granules. The open arrow (right) shows an adjacent labeled nuclei. The positions of the corneal endothelium (CE), anterior trabecular insert into the cornea (TM), and the corneal stroma (CS) are shown. Photomicrographs were taken with a 100× objective and oil immersion.

covered with cells and appeared less ordered than those in areas not treated by laser. Immediately after laser treatment, spots of approximately 150 μm in diameter were completely denuded at the burn sites.

The percentage of cells that were labeled within the total meshwork was increased approximately fourfold by laser treatment over controls at the zero-day chase period ($P < .001$) (Fig. 3). A slight decrease was observed after seven or 14 days of chase; however, these values were still significantly increased compared to controls ($P < .02$ and $P < .01$, respectively). Since the zero-, seven-, and 14-day chase controls were not significantly different from each other, they were pooled for this figure. When the total meshwork was subdivided into two regions, the anterior and the posterior (Fig. 3), it was apparent that immediately after radiolabeling (at zero days' chase) most of the radiolabeled nuclei were localized in the anterior portion of the meshwork. This zero-day chase shows an increase of approximately sixfold over controls ($P < .001$). By seven or 14 days of chase, however, the percentage of labeled nuclei found in the anterior portion of the meshwork had declined and was not significantly increased above control levels. Concomitant with this decline was an increase in the percentage of labeled nuclei found in the posterior portion of the laser-treated meshwork at seven and 14 days.

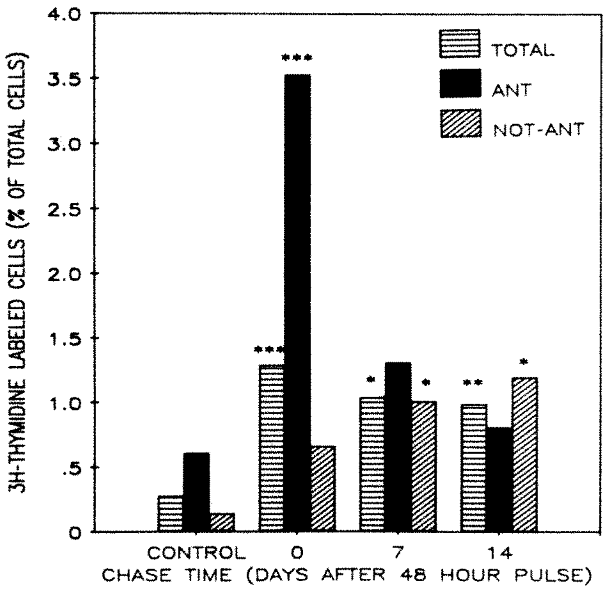

Fig. 3 (Acott and associates). Chase time course, after 48-hour labeling with ^{3}H-thymidine immediately after laser or control treatment, showing the percentage of cells that had more than 20 grains over their nuclei. Total is the data for the total meshwork including the anterior insert region and Schlemm's canal; Ant is the anterior insert region of the meshwork only; Not-Ant is the total meshwork excluding the anterior region. The * indicates a difference from control with $P < .02$; the ** indicates $P < .01$; and the *** indicates $P < .001$ as determined using Student's *t*-test. Each time point is the mean from the analysis of between six and 14 slides, with 16 sections per slide and at least three separate explants. The average number of trabecular cells per section was 80. Because the laser-treated and nonlaser-treated portions of the treated explants were not significantly different from each other, they were also pooled in this figure.

These data suggest a shift in regional distribution of labeled nuclei with chase time. To evaluate this shift in more detail, we determined the relative distribution of labeled nuclei within the four regions of the meshwork as defined earlier. A decline in labeled nuclei in the anterior region (from 56% at zero days to 26% at 14 days) was associated with a concomitant increase in labeled nuclei in the burn region (from 7% to 60%) (Fig. 4). The increased label density in the burn area at seven and particularly at 14 days was only observed in the laser-treated portions, not in the nonlaser-treated portions, of the treated explants.

The controls showed a low but significant level of basal cell division (Fig. 3). As with the laser trabeculoplasty-stimulated meshwork, at least half of the basal cell divisions were observed in the anterior insert region of the meshwork. The region of Schlemm's canal contributed about half of the remainder of the basal divisions. No changes in distribution during the control chases were observed.

To obtain a more macroscopic view of the temporal changes in labeled nuclei distribution, we developed ^{14}C-thymidine macroautoradiographs of whole explants after zero- and 14-day chase periods. Micrographs taken through a dissecting scope of a laser-treated, 14-day chase meshwork showed a focused trail of label grains moving out from the anterior meshwork toward the burn sites (Fig. 5). The radial location and distance interval between laser burns applied to the explant, based on measurements made during the laser treatment rather than observable burn sites, showed a positional relationship between burns and the

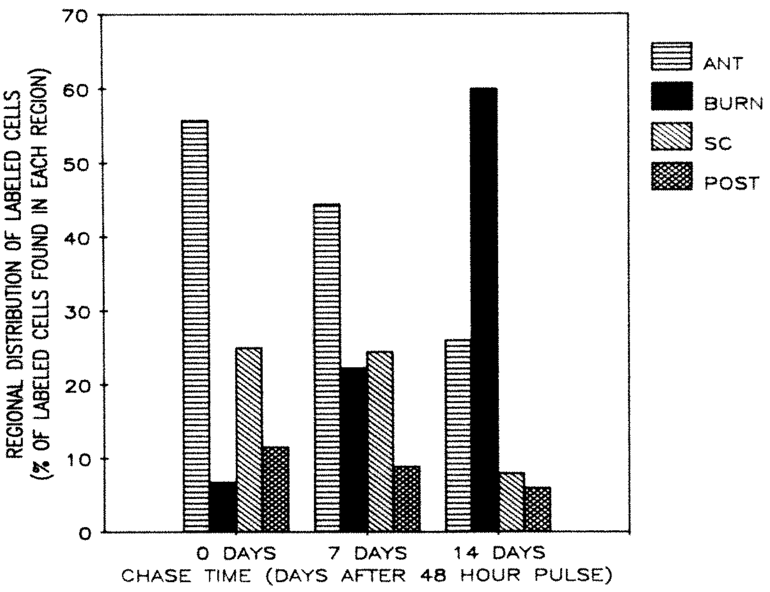

Fig. 4 (Acott and associates). Analysis of the regional distribution of radiolabeled nuclei at each point in the chase time course. At each time, the number of labeled nuclei found in each of the regions is presented as a percentage of the labeled nuclei found in the total meshwork at that time.

focused trails of label grains. At zero days of chase, no localized grain pattern was observed (data not shown).

Discussion

Laser trabeculoplasty produces a dramatic increase in cell division (approximately sixfold) within an apparently specialized population of cells, which are located anterior to the filtering portion of the meshwork in the triangular region where it inserts into the cornea, within the first 48 hours after treatment. By 14 days 60% of these labeled cells are found near the laser burn sites. We hypothesize that these freshly divided cells migrate from their origin in the anterior meshwork to repopulate the burn sites. Although we did not observe this migration directly, the magnitude of the changes in the distribution of labeled cells is difficult to explain by any alternative hypothesis. Additionally, the total number of labeled cells found in this anterior insert region (approximately 60 per ten slides) for the zero-day chase, the decrease in this region to around 30 by 14 days of chase, and the appearance of around 35 labeled cells (per ten slides) in the burn region by 14 days support a migratory repopulation hypothesis.

In control explants, the basal cell division is localized primarily to this anterior, nonfiltering region of the trabeculum. This region appears to be more compact, with minimal intratrabecular spaces, but the cells clearly resemble those of the trabeculum proper more than they do those of the adjacent corneal endothelium or stroma. This anterior region of the meshwork's insertion into the cornea has been described by others[12,13] and the cells are thought to express somewhat different biochemical properties.[12] Our observations would support, although not

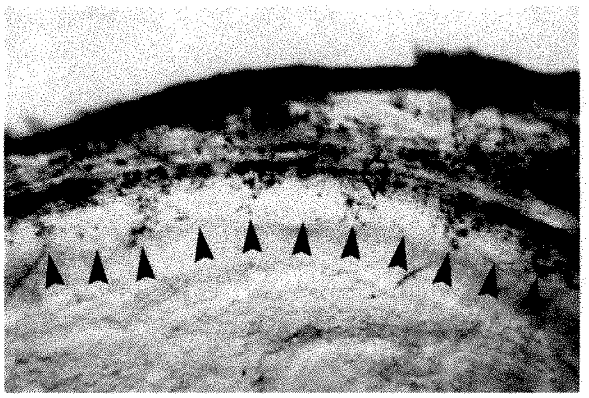

Fig. 5 (Acott and associates). Photomicrograph of ^{14}C-thymidine macroautoradiography of a laser-treated explant after a 14-day chase. The arrows indicate the sites of laser burns as estimated from measurements of their spacing; the burns were placed centered over the lower pigment line (open arrow) ($\times 30$).

prove, that this population of cells is less differentiated, perhaps serving as a pluripotent or "stem cell" for the meshwork under normal conditions or perhaps only after laser trabeculoplasty or other forms of trabecular wounding. An analogous but external limbal stem cell for corneal epithelial wound repopulation has been identified recently.[14,15]

Although only one half (180 degrees) of the trabecular meshwork was treated by laser trabeculoplasty, the initial 48-hour burst of cell division is not significantly different, when sections from the laser-treated and nonlaser-treated portions are compared. Clinically, patients show similar aqueous humor outflow changes in response to laser trabeculoplasty, whether treatments are over 180 or 360 degrees.[16-18] Our data support the idea that the regulatory signal for cell replication is medium-born.

The simplest hypothesis compatible with our data is that within the first 48 hours after laser trabeculoplasty, a specific population of anterior trabecular cells divides. Then, over the next few weeks these cells migrate into and repopulate the laser burn sites. Presumably, this repopulation is involved in the return to normal intraocular pressures and aqueous humor outflow rates.

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Effects of Carbachol and Acetylcholine on Intraocular Pressure After Cataract Extraction

Richard S. Ruiz, M.D., Marcus N. Rhem, and Thomas C. Prager, Ph.D.

We compared the effect of carbachol and acetylcholine on intraocular pressure 24 hours after extracapsular cataract extraction. All agents were administered intracamerally at the time of surgery. Sixty patients scheduled for routine extracapsular cataract extraction and intraocular lens implantation were randomly assigned into one of three treatment groups: (1) carbachol, (2) acetylcholine, or (3) 0.5% balanced salt solution (placebo). Baseline intraocular pressures were determined the day before surgery, and postoperative pressures were measured approximately 24 hours after surgery. The group intraocular pressures averaged over preoperative and postoperative values were 21.06 mm Hg in the acetylcholine group, 19.36 mm Hg in the control group, and 17.30 mm Hg in the carbachol group. The average difference between preoperative and postoperative intraocular pressure measurements for the three groups were 7.33 mm Hg for the acetylcholine group, 8.73 mm Hg for the control group, and 2.20 mm Hg for the carbachol group. Only carbachol was significantly different from placebo on statistical subsequent testing. Carbachol is suggested as the agent of choice both for achieving intrasurgical miosis and prophylaxis of increasing intraocular pressure after cataract surgery.

TRANSITORY INCREASE in intraocular pressure after cataract surgery[1-3] may cause pain and corneal edema and may contribute to ischemic optic neuropathy.[4] Consequently, intraocular hypertension immediately after surgery continues to be of clinical interest.

We performed a randomized, masked study to compare the effect of carbachol and acetylcholine on intraocular pressure 24 hours after extracapsular cataract extraction. All drugs were administered intracamerally at the time of surgery.

Material and Methods

Patients scheduled for routine extracapsular cataract extraction and posterior chamber lens implantation were randomly assigned to one of three treatment groups: (1) carbachol, (2) acetylcholine, or (3) 0.5% balanced salt solution (control). A sample size of 60 patients, 20 per group, was determined adequate to demonstrate statistically a separation of 2 mm Hg (alpha = 0.05, beta = 0.10).[5] Patients were admitted into the study after meeting the following criteria: no history of intraocular surgery, retinal detachment, or uveitis; no history of glaucoma or long-term use of ocular medications; no record of intraocular pressure exceeding 22 mm Hg; and no contraindication to the use of a posterior chamber intraocular lens. All patients underwent extracapsular cataract extraction and implantation of a Sinsky-type posterior chamber lens performed by one of us (R.S.R.). Retrobulbar anesthesia was used. Mydriasis was induced preoperatively by three applications of tropicamide 1% and phenylephrine 2.5% given at 15-minute intervals, with intrasurgical irrigation of epinephrine into the anterior chamber to increase pupillary dilation further. The nucleus was removed with a lens loop and the cortex was removed by irrigation and aspiration, using balanced salt solution. Air was placed in the anterior chamber before implantation of the intraocular lens. No viscoelastic substance was used. After insertion of the posterior chamber lens, 1 ml of carbachol, 1 ml of acetylcholine, or 1 ml of balanced salt solution was irrigated into the anterior cham-

Accepted for publication Oct. 4, 1988.
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ber. Each patient was selected in a randomized fashion. A watertight closure of the surgical incision was made using four interrupted 10-0 Prolene sutures and two 8-0 Vicryl sutures.

Baseline intraocular pressure readings were determined between 8 A.M. and 2 P.M. on the day before surgery. Postoperative pressures were measured approximately 24 hours after surgery. All intraocular pressure measurements were made by the same individual who was masked to each patient's treatment category. Three measurements were taken with the same Goldmann tonometer, orienting the tonometer prism horizontally and vertically to minimize error from induced astigmatism. Measurements were repeated after waiting five minutes, thus avoiding an artifactual decrease in intraocular pressure between consecutive measurements. Measurements were taken until three consecutive readings varied less than 2 mm Hg, then averaged and recorded.

Results

Intraocular pressure averaged over preoperative and postoperative trials were 21.06 mm Hg in the acetylcholine group, 19.36 mm Hg in the control group, and 17.30 mm Hg in the carbachol group (Fig. 1). To determine whether there was a statistically significant difference for groups and for time of measurement a repeated measure subject nested in group by trial analysis of variance[6] was conducted since each patient contributed two data points (preoperative and postoperative values) and was in one of three randomly assigned treatment groups. There was a significant difference among groups ($F = 3.89$, $P = .026$) and a highly significant difference between preoperative and postoperative intraocular pressure values ($F = 49.59$, $P < .0001$). Furthermore, the mean and associated variabilities for the three groups were significantly greater at 24 hours after surgery than before surgery as evidenced by a significant group by time (trial) interaction[6] ($F = 5.27$, $P = .008$).

This same trend was found in another statistical analysis. The differences in intraocular pressure before and after surgery were 7.33 mm Hg in the acetylcholine group, 8.73 mm Hg in the control group, and 2.20 mm Hg in the carbachol group (Fig. 2). A one-way analysis of variance demonstrated a significant difference among groups ($F = 5.27$, $P = .008$) and a Newman-Keul's multiple range subsequent test demonstrated that only carbachol was significantly different than placebo ($P < .05$).

Discussion

Increased intraocular pressure has been noted after cataract surgery even in patients with no history of glaucoma.[1-3] Accordingly, the routine use of postoperative prophylactic therapy should be beneficial, particularly if this treatment does not add significantly to morbidity or expense.

Most cataract surgeons desire pupillary constriction after placement of an intraocular lens to assure appropriate positioning of the im-

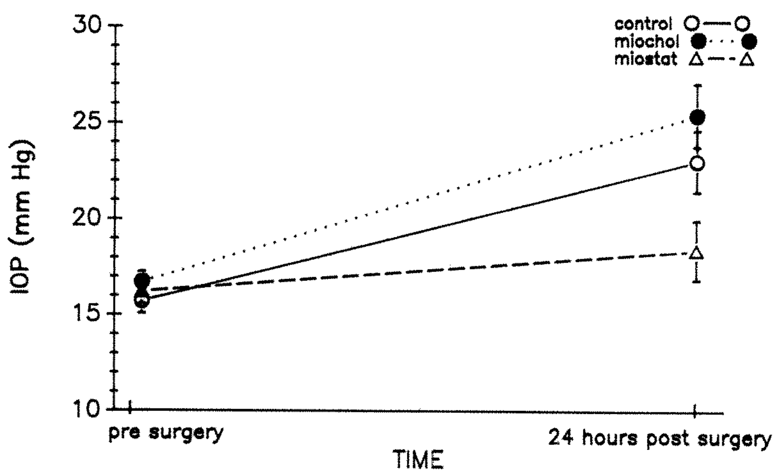

Fig. 1 (Ruiz, Rhem, and Prager). Mean ± 1 S.D. intraocular pressure before and 24 hours after surgery. Miochol, acetylcholine; Miostat, carbachol; IOP, intraocular pressure.

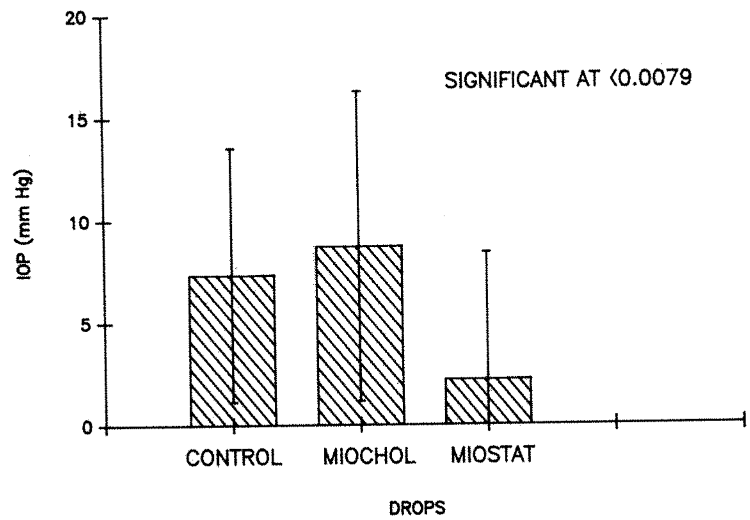

Fig. 2 (Ruiz, Rhem, and Prager). Mean ± 1 S.D. difference in intraocular pressure (value 24 hours after surgery minus value before surgery).

planted lens and a free, unencumbered iris. In most cases, pupillary constriction has been achieved at the time of surgery through the administration of intracameral acetylcholine. Timolol or carbonic anhydrase inhibitors are usually used postoperatively to control intraocular pressure.[7-12] An agent that could effect adequate miosis intraoperatively and control of intraocular pressure postoperatively would be desirable both therapeutically and economically. Ruiz and associates[13] found that topically applied pilocarpine gel used in this capacity reduced postsurgical intraocular pressure significantly. However, pilocarpine may produce ciliary spasm that can be uncomfortable for some patients.[14] In rare cases, headaches and twitching as well as more severe systemic side effects have been reported that may be related to the misuse of the drug.[15] Timolol and pilocarpine eyedrops were not effective in reducing intraocular pressure at 24 hours when compared to controls.[13]

Hollands, Drance, and Schulzer[16] investigated the efficacy of acetylcholine in the postoperative management of intraocular pressure and found it to have no significant effect beyond six hours from the time of surgery. In a separate study,[17] they examined the use of carbachol postoperatively and found the intraocular pressure to be significantly lower at 24 hours.

In our study, carbachol appeared to be a potent intraoperative miotic equal to acetylcholine. Carbachol was also efficacious in the management of intraocular pressure at 24 hours after surgery when compared to placebo. Intracameral carbachol was shown to be significantly more effective than intracameral acetylcholine in this regard, indicating that carbachol should be the treatment of choice for prophylaxis of postsurgical increase in intraocular pressure. Carbachol exerts systemic action that may lead to various undesirable side effects, many of which are similar to those associated with pilocarpine.[15] Most of these effects are correlated with prolonged use of the drug. In this study, where the drug was used intraoperatively, side effects were not significant.

Both carbachol and pilocarpine gel have been shown to be statistically superior to timolol and acetazolamide in controlling intraocular pressure postoperatively. The superiority of carbachol over acetylcholine in controlling transitory increases in intraocular pressure after cataract surgery, as demonstrated by this study and others, suggests that carbachol is the miotic of choice even in routine cataract extractions performed on patients with no history of glaucoma. There is also evidence that carbachol is less toxic to the corneal endothelium than acetylcholine.[18] For patients with a history of glaucoma, the application of pilocarpine gel in addition to the intrasurgical use of carbachol should prove to be particularly effective in controlling intraocular pressure after cataract surgery.

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OPHTHALMIC MINIATURE

. . . a drop of rain water hangs at the tip of a leaf
Shifting in the wakening sunlight
Like the eye of a new-caught fish.

Theodore Roethke, "The Rose," Part III

Intraocular Pressure Effects of Carbonic Anhydrase Inhibitors in Primary Open-Angle Glaucoma

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We tested the effect on intraocular pressure of three commonly used oral carbonic anhydrase inhibitor preparations in a controlled, randomized, comparative study on patients with primary open-angle glaucoma. Preparations tested included acetazolamide tablets, acetazolamide Sequels, and methazolamide tablets. The effect of the three carbonic anhydrase inhibitors was assessed by using a statistical modeling approach as well as by evaluating the average maximum reduction in intraocular pressure for each preparation. Dosage and time effects were also determined. As expected, each drug preparation was more effective in reducing intraocular pressure when administered to a patient who had already been treated with the carbonic anhydrase inhibitor preparation. The amount of intraocular pressure lowering was directly related to dose for both acetazolamide preparations. Of particular interest was the finding that maximal rapid reduction of intraocular pressure was obtained with a 500-mg dosage of acetazolamide tablets.

CARBONIC ANHYDRASE INHIBITORS have been used for over 30 years in the treatment of glaucoma.[1,2] Of a number of carbonic anhydrase inhibitors proposed for human use, acetazolamide and methazolamide have been clinically widely used in lowering intraocular pressure. Although there is no doubt that these agents significantly reduce intraocular pressure in normal volunteers,[3] ocular hypertensives,[4,5] and patients with various forms of glaucoma,[6-8] comparative studies of the effects of different carbonic anhydrase inhibitor preparations and the effects of the different doses of each on intraocular pressure lowering are needed. In light of current efforts to develop a clinically efficacious topical carbonic anhydrase inhibitor,[9-17] data on oral agents can serve as a yardstick against which the effectiveness of topical agents is measured.

The purpose of this study was to evaluate the intraocular pressure effects of three commonly used carbonic anhydrase inhibitor preparations in the patient group in which the drugs are most commonly used, open-angle glaucoma patients in whom topical therapy has failed to control their intraocular pressure.

Patients and Methods

Nineteen patients from the Glaucoma Service of the Kellogg Eye Center, University of Michigan, were recruited for this study. All of these patients had a confirmed diagnosis of primary open-angle glaucoma, with visual field loss and optic disk damage. Each patient was using maximum tolerated pilocarpine and epinephrine before the study, with evidence of poor control of intraocular pressure (>20 mm Hg), and some were also using carbonic anhydrase inhibitors. Patients with a history of liver or kidney disease, altered serum electrolytes, or hypersensitivity to sulfonamides, as well as those using systemic corticosteroids, thiazide diuretics, digitalis preparations, or high doses of aspirin were not eligible for the study. Four of the 19 patients were excluded from the study because of intolerable carbonic anhydrase inhibitor side effects, poor compliance, or use of nonprotocol topical medications during the

Accepted for publication Sept. 28, 1988.
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course of the study. Therefore, 15 patients completed the study, seven men and eight women, with a mean age of 64.1 years (S.D., 6.8 years; range, 49 to 77 years).

Upon recruitment and determination of eligibility, the patients were randomly assigned to one of three groups, in which acetazolamide tablets (Diamox), methazolamide tablets (Neptazane), and acetazolamide sustained-release capsules (Diamox Sequels), respectively, were used. The patients were instructed to discontinue all previously used carbonic anhydrase inhibitor medications, and to use epinephrine hydrochloride 2% (Epifrin) twice a day and pilocarpine hydrochloride 4% (various brands) four times a day. Two baseline visits were conducted, at which intraocular pressure was monitored over a period from 8:00 A.M. to 5:00 P.M. If the intraocular pressure was not at least 20 mm Hg during the baseline visits, the patient would have been ineligible for continuing the study. All of the recruited patients met this criterion. Beta-adrenergic blocking agents were not used as a topical therapy in this study, since these compounds significantly reduce aqueous production and would confound the effectiveness of carbonic anhydrase inhibitor agents in reducing intraocular pressure.

Upon completion of the baseline visits, the patients went through a series of drug visits, in which both the study condition and the dose were randomly determined. For acetazolamide tablets, three doses were used (125, 250, and 500 mg) under three different study conditions: no pretreatment with the test drug, single administration of four times the test drug dose 18 hours before the drug visit, and pretreatment with the test drug dose four times a day (8:00 A.M., 12 noon, 5:00 P.M., and 10:00 P.M.) for the two days preceding the visit. For methazolamide tablets, three doses were used (25, 50, and 100 mg) under the same three study conditions. For acetazolamide sustained-release capsules, two doses were used (500 and 1,000 mg) under the three previously described study conditions (with the exception of an alteration in the two-day pretreatment scheme, which was changed from taking the test drug four to two times a day, 8:00 A.M. and 8:00 P.M. for the two days preceding the visit). Because of the investigators' concern for possible side effects, the largest dose for the 18-hour pretreatment condition in each drug was not administered. Therefore, each patient who received acetazolamide or methazolamide tablets went through a sequence of eight drug visits, with eight different pretreatment/dose combinations, and those receiving acetazolamide sustained-release capsules had five drug visits, with five different pretreatment/dose combinations. A washout period was required between drug visits to avoid residual drug effects from one regimen to the next. The length of this period was specified to be at least four days when the preceding visit involved no pretreatment, and at least seven days when the preceding visit involved drug pretreatment.

A typical visit began at 8:00 A.M., with the verification of the study condition and measurement of intraocular pressure. The randomly determined test dose was then administered, and intraocular pressure assessments were performed at 9:30 A.M., 11:00 A.M., 2:00 P.M., and 5:00 P.M.

In order to assess the independent effects of the dose, pretreatment, and time conditions on intraocular pressure, a three-way analysis of variance model was applied to the eye-specific data from each patient. The resulting dose-, pretreatment-, and time-specific coefficients for the five patients on each carbonic anhydrase inhibitor were then averaged, and their significance was tested using a one-sample t-test. Since the incomplete block design of the study did not allow for a perfect factorial experiment, in which assessment of interaction between dose and treatment could be achieved in the analysis of variance model, this effect was assessed by fitting a one-way analysis of variance model, which evaluated the intraocular pressure effect of the eight dose/pretreatment combinations separately. Since no interaction was evident between dose and pretreatment conditions upon contrasting these models, only the results of the three-way analysis of variance model will be detailed.

Results

Time-specific, baseline intraocular pressure values (Table 1) for the patients in each drug group were contrasted with measurements taken throughout the day after each drug regimen was tested.

Application of the statistical model to the intraocular pressure data gathered on the 15 patients who completed the study allowed for the separate evaluation of dose, pretreatment, and time effects for the three carbonic anhy-

TABLE 1
TIME-SPECIFIC BASELINE INTRAOCULAR PRESSURE BY DRUG GROUPS

DRUG GROUP*	MEAN (RANGE) INTRAOCULAR PRESSURE AT BASELINE VISIT (MM HG) 8:00 A.M.	9:30 A.M.	11:00 A.M.	2:00 P.M.	5:00 P.M.
Acetazolamide tablets	20 (15–24)	21 (16–26)	24 (16–31)	20 (14–25)	22 (17–29)
Acetazolamide time-release capsules	22 (16–28)	23 (16–32)	24 (18–31)	19 (13–28)	20 (15–26)
Methazolamide	26 (23–29)	26 (23–31)	29 (25–33)	23 (20–27)	25 (19–29)

*Each group consisted of five patients, two baseline visits per patient.

drase inhibitor drugs administered in the study. Table 2 shows the average effect of these factors on intraocular pressure for the three drugs. A consistent, positive dose-response effect was seen for the two acetazolamide drugs. A statistically significant lowering of intraocular pressure was found at each dose level of the acetazolamide drugs, which was consistent for the separate analyses of the right and left eyes. Methazolamide, however, had such a variable intraocular pressure effect that no dose showed a statistically significant intraocular pressure effect. Pretreatment effects were most pronounced for the two drugs that were not administered in a timed-release form: acetazolamide tablets and methazolamide. An independent time effect on intraocular pressure was most evident during the afternoon measurements, which may reflect diurnal influences.

The maximum reduction of intraocular pressure from baseline measurements following carbonic anhydrase inhibitor administration, in absolute and percent reduction, is shown in Table 3. The range of maximum intraocular pressure reduction for acetazolamide tablets was from 7.0 to 9.9 mm Hg (30.0% to 40.6%), for acetazolamide sustained-release capsules, from 4.9 to 7.2 mm Hg (22.1% to 32.0%), and for methazolamide, from 2.0 to 8.5 mm Hg (7.1% to 33.0%). These results dealt with only one intraocular pressure measurement per patient, the maximum reduction in intraocular pressure after carbonic anhydrase inhibitor administration, while the analysis of variance model addressed all intraocular pressure measurements throughout the visit. Both approaches corroborate a positive, dose-response effect for the three carbonic anhydrase inhibitors tested.

To demonstrate the effect of these carbonic anyhydrase inhibitor regimens over the course of the visit, the average percent change from

TABLE 2
DOSE, PRETREATMENT, AND TIME EFFECTS ON INTRAOCULAR PRESSURE FOR THE THREE CARBONIC ANHYDRASE INHIBITORS TESTED

	ACETAZOLAMIDE TABLETS			ACETAZOLAMIDE TIME-RELEASE CAPSULES			METHAZOLAMIDE		
		R.E.	L.E.		R.E.	L.E.		R.E.	L.E.
Dose effect (mean [S.D.] in mm Hg)	125 mg	−3.7 (2.1)*	−3.0 (1.5)*	500 mg	−3.6 (2.7)†	−2.3 (1.4)*	25 mg	0.2 (4.2)	2.0 (5.3)
	250 mg	−4.2 (2.5)*	−4.4 (2.5)*	1,000 mg	−4.0 (1.6)*	−2.9 (0.9)*	50 mg	0.9 (3.7)	1.5 (5.1)
	500 mg	−5.1 (2.6)*	−6.0 (2.1)*				100 mg	−1.9 (3.7)	−1.5 (3.9)
Pretreatment effect (mean [S.D.] in mm Hg)	18 hr	−2.0 (1.1)*	−2.7 (2.1)*		−2.8 (2.8)	−2.8 (2.4)		−3.3 (2.0)*	−3.9 (2.3)*
	48 hr	−1.4 (1.6)	−1.7 (1.0)*		−2.3 (1.0)*	−2.2 (1.4)†		−4.7 (1.7)*	−4.5 (1.7)*
Time effect (mean [S.D.] in mm Hg)	9:30 AM	−0.2 (1.1)	0.0 (1.6)		−0.7 (1.5)	−0.8 (1.2)		−0.3 (2.4)	−1.1 (2.2)
	11:00 AM	1.6 (2.4)	1.6 (1.2)		−1.2 (1.8)	−1.0 (1.0)		1.8 (2.0)	0.7 (1.1)
	2:00 PM	−1.5 (1.5)	−1.7 (1.8)		−4.4 (0.8)*	−3.5 (0.7)*		−3.7 (3.2)†	−3.8 (2.2)*
	5:00 PM	0.6 (2.5)	0.1 (1.1)		−3.3 (0.3)*	−2.9 (1.5)*		−1.3 (1.9)	−1.3 (1.5)

*$P < .05$, for the test of a significant intraocular pressure lowering from baseline measurements.
†$.05 < P < .10$.

TABLE 3
MAXIMUM INTRAOCULAR PRESSURE REDUCTION AFTER ADMINISTRATION OF CARBONIC ANHYDRASE INHIBITOR*

	ACETAZOLAMIDE TABLETS			ACETAZOLAMIDE SUSTAINED-RELEASE CAPSULES			METHAZOLAMIDE		
	DOSAGE (MG)	MEAN (S.D.) ABSOLUTE	MEAN (S.D.) PERCENT	DOSAGE (MG)	MEAN (S.D.) ABSOLUTE	MEAN (S.D.) PERCENT	DOSAGE (MG)	MEAN (S.D.) ABSOLUTE	MEAN (S.D.) PERCENT
No pretreatment	125	7.0 (3.3)	30.0 (10.7)	500	4.9 (2.9)	22.1 (11.2)	25	3.2 (2.8)	13.5 (11.4)
	250	8.4 (2.8)	35.2 (8.1)	1000	6.2 (1.5)	31.2 (7.6)	50	2.0 (3.9)	7.1 (13.9)
	500	8.8 (3.5)	35.6 (5.6)	—	—	—	100	6.5 (4.9)	22.7 (16.6)
18-hr pretreatment	125	9.1 (2.3)	36.9 (9.4)	500	7.2 (1.7)	32.0 (9.6)	25	5.0 (3.6)	19.7 (13.2)
	250	9.4 (2.3)	40.0 (5.0)	—	—	—	50	4.6 (2.0)	17.5 (6.4)
48-hr pretreatment	125	8.2 (3.5)	35.0 (7.3)	500	5.5 (2.2)	26.8 (10.9)	25	7.0 (2.4)	27.0 (9.2)
	250	8.5 (2.5)	34.8 (5.6)	1000	6.5 (1.2)	30.7 (7.3)	50	5.9 (2.7)	22.0 (9.6)
	500	9.9 (4.1)	40.6 (9.1)	—	—	—	100	8.5 (2.5)	33.0 (8.0)

*Right eye only, n = 5, all figures expressed as mean (S.D.) in mm Hg.

the 8:00 A.M. intraocular pressure measurement (on the visit day) is presented in Figures 1 through 3 for the non-pretreatment regimens. Since a washout period was required before the visit, and no pretreatment doses were given, these data represent acute intraocular pressure effects resulting from carbonic anhydrase inhibitor administration in a carbonic anhydrase inhibitor-free glaucoma patient, as contrasted with the intraocular pressure pattern during the baseline visits in which no carbonic anhydrase inhibitor was given.

All acetazolamide tablet doses showed an initial repression of the baseline diurnal intraocular pressure increase from 8:00 A.M. to 9:30 A.M. (Fig. 1). This effect continued through 11:00 A.M. only for the 500-mg dose. While the remaining pattern for each dose over the visit day paralleled the baseline intraocular pressure curve, the beneficial intraocular pressure effect of each dose is reflected by the downward displacement of the treatment intraocular pressure curve relative to the baseline intraocular pressure curve. Both acetazolamide sustained-release doses caused a reversal of the baseline increase in intraocular pressure over the first three hours of the visit day (Fig. 2). The only methazolamide dosage that showed a similar effect was the 100-mg dose (Fig. 3).

Discussion

A consistent, positive dose-response effect on intraocular pressure was observed for both acetazolamide preparations used in the study, whereas the intraocular pressure effect of the three methazolamide dosages administered was subject to considerable variation. Upon inspecting the patient-specific results from the five patients receiving methazolamide, it was

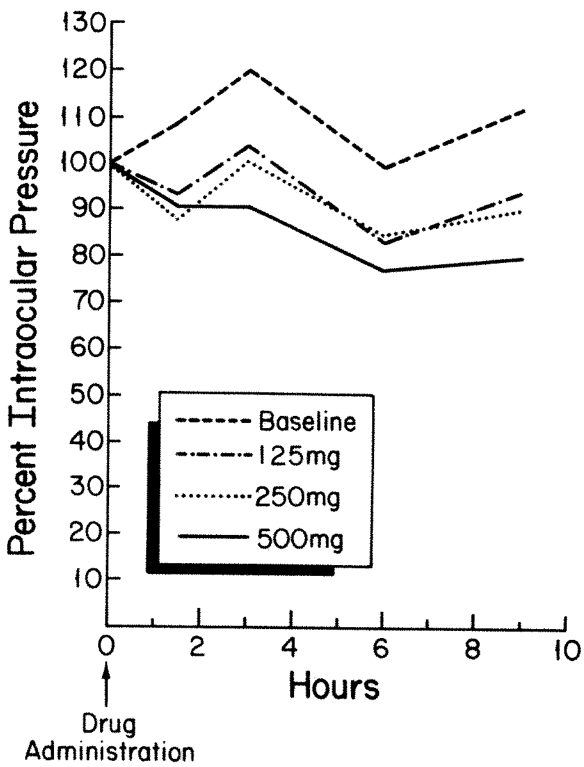

Fig. 1 (Lichter and associates). Change in intraocular pressure after oral administration of acetazolamide tablets.

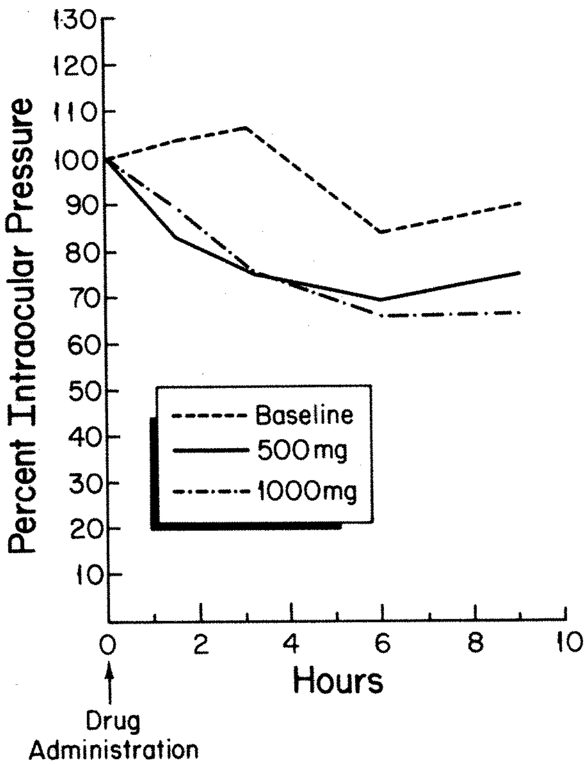

Fig. 2 (Lichter and associates). Change in intraocular pressure after oral administration of acetazolamide sustained-release capsules.

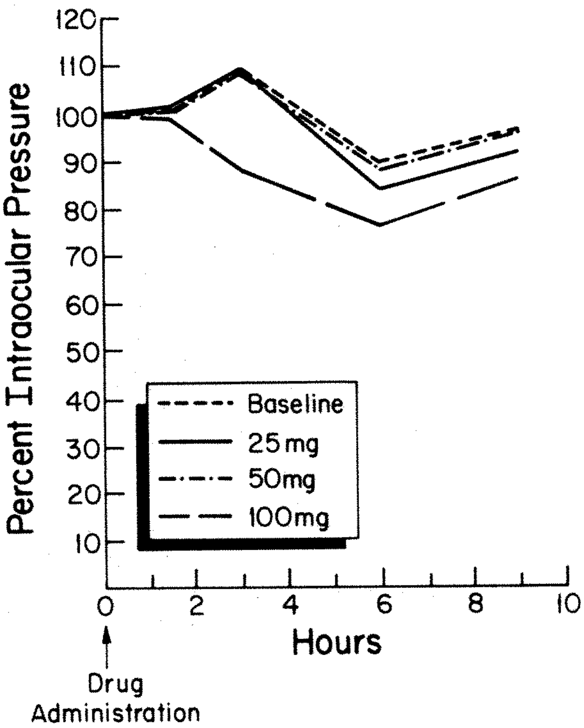

Fig. 3 (Lichter and associates). Change in intraocular pressure after oral administration of methazolamide.

evident that this result was caused by a variable response to this drug, similar to that found by Dahlen and associates.[8] One patient did not respond to any of the three methazolamide dosages, and actually demonstrated intraocular pressure values well above the baseline visit measurements. Two additional patients showed no response to the 50-mg dose, which contributed to the finding of a minimal intraocular pressure effect at this dosage. With a total of only five patients taking each carbonic anhydrase inhibitor, this variable response to methazolamide substantially affected the results.

Both pretreatment schemes had a significant intraocular pressure-lowering effect that was independent of the dose effect and evident for all three carbonic anhydrase inhibitor drugs. The pool of carbonic anhydrase in erythrocytes must be saturated by the inhibitor drug before a substantial effect on ciliary body carbonic anhydrase[18]; therefore, the effect of these pretreatment schemes is to be expected. Pretreatment with methazolamide had the greatest impact on intraocular pressure, and this may relate to the longer half-life of methazolamide in the system (14 hours reported after an oral dose) relative to acetazolamide (five hours reported after an oral dose).[18]

While washout intervals in this study were set to allow sufficient time for elimination of previously administered carbonic anhydrase inhibitor from the patient's body, low levels of the drug were detectable in the blood samples of some patients in the study after their washout period. The effect of such occurrences would be to diminish any intraocular pressure lowering effect of the next drug regimen. Since the next regimen was randomly determined for each patient, insufficient washout should not produce a systematic bias into the study, but rather may have reduced the study's ability to detect a true drug effect on intraocular pressure.

While several investigators have attempted to identify the optimal chronic dosage of carbonic anhydrase inhibitors,[5-8] ophthalmologists are also faced with situations requiring acute reduction of intraocular pressure. Our results indicated that acetazolamide preparations had a greater initial effect on intraocular pressure

than methazolamide. Furthermore, a dose of 500-mg acetazolamide tablets with no previous treatment resulted in the largest intraocular pressure lowering effect (average maximal lowering, 8.8 mm Hg [35.6%]) in the shortest period of time. This result provides additional support to an earlier report that 250 mg of methazolamide had a slower action on intraocular pressure reduction than 250 mg of acetazolamide.[19] We therefore recommend use of 500 mg of acetazolamide in tablet form in a situation where rapid intraocular pressure reduction is required from an oral agent. Intravenous administration of acetazolamide would likely be still more effective, but this was not tested in the present study.

Determination of the optimal chronic carbonic anhydrase inhibitor dosage is a more difficult matter. Many factors enter into this decision, including the ability of the individual patient to tolerate the well-documented side effects of carbonic anhydrase inhibitor drugs,[20-22] as well as the effect on intraocular pressure. Although not tested in this study, the potential of a beneficial response to combined carbonic anhydrase inhibitor/beta-adrenergic blocker therapy[23-29] should be considered, and may influence the selection of an appropriate, patient-specific carbonic anhydrase inhibitor dosage.

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Ophthalmic miniature

Besides, the eyes of the understanding see best when those of the senses are out of the way, and therefore, blind men are observed to tread their steps with much more caution, and conduct, and judgment, than those who rely with too much confidence upon the virtue of the visual nerve, which every little accident shakes out of order, and a drop or a film can wholly disconcert, like a lantern among a pack of roaring bullies when they scour the streets, exposing its owner and itself to outward kicks and buffets, which both might have escaped if the vanity of appearing would have suffered them to walk in the dark.

Jonathan Swift, "A Tale of A Tub"

Intraocular Pressure After Cardiopulmonary Bypass Surgery

David Deutch, M.D., and Richard A. Lewis, M.D.

The ocular effects of cardiopulmonary bypass surgery were prospectively studied in 46 patients. We examined preoperative and postoperative visual acuity, intraocular pressure, body weight, fluids infused during surgery, hematocrit, and cardiopulmonary bypass time. On the first postoperative day mean intraocular pressure increased 2.1 mm Hg (P = .003) from baseline preoperative levels. Over the first postoperative day intraocular pressure increased in 29 (63%) of the patients. Three patients (7%) had a greater than 10 mm Hg rise. The mean intraocular pressure returned to baseline by the third postoperative day. Patient weight increased from preoperative levels an average of 9.3 lbs (P < .0001) on day 1 and 6.5 lbs on day 3. Mean hematocrit decreased 11.3% (P < .0001) on day 1 from baseline and remained at that level through day 3. None of the patients complained of visual dysfunction during the course of this study and none showed more than a two-line decrease in near visual acuity. The increase in intraocular pressure did not correlate with the postoperative weight gain or hemodilution. However, the medications necessary after cardiac surgery may be a significant confounding variable. This study demonstrates that one cause of ocular problems from cardiopulmonary bypass surgery may be related to the dynamics of intraocular pressure.

OCULAR COMPLICATIONS after cardiac surgery with cardiopulmonary bypass have been reported in up to 25% of patients.[1] These problems have been attributed to the variety of physiologic changes that occur during cardiac surgery, including systemic hypotension, cerebral hypoperfusion, embolic phenomena, and hypothermia.[1,2] An additional problem that has not been extensively studied is the effect of large fluid infusions used during cardiopulmonary bypass. These patients routinely receive up to 8 liters of intravascular fluid volume during the course of a one- to four-hour operation. Large fluid infusions have an effect on intraocular pressure and Larkin and associates[3] showed a rapid intraoperative rise in intraocular pressure during bypass circulation. However, there have been no detailed studies on intraocular pressure after cardiopulmonary bypass surgery. This prospective study seeks to determine the duration of intraocular pressure increase after cardiopulmonary bypass surgery and its effect on visual acuity.

Patients and Methods

Fifty patients consecutively admitted for elective cardiopulmonary bypass surgery were included in this prospective study. One patient was excluded because of additional unrelated surgery at the time of bypass surgery. Three patients were excluded because of inability to measure intraocular pressure on the first postoperative day. Previous ocular or medical history was not an exclusion criterion.

Preoperative examination occurred on the morning of surgery and postoperative examinations were made on days 1, 2, and 3. All examinations were performed between the hours of 6:30 and 9:00 A.M. at the patients' bedside by the same examiner (D.D.).

Preoperatively, patients were questioned about previous ocular disease. Intraocular pressure was determined by using the Perkins applanation tonometer in the initial 19 patients, and the Tono-pen tonometer in 27 patients. Once the patient was enrolled in the

Accepted for publication Oct. 3, 1988.

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study the same tonometer was used throughout. The mean intraocular pressure readings of the right and left eyes were used for this study.

Review of each patient's medical chart determined the amount of intravenous fluids administered, the duration of cardiopulmonary bypass, daily body weight (not measured on postoperative day 1 while patient was in the intensive care unit), daily hematocrit, and preoperative and postoperative medications.

A paired *t*-test was used for statistical analysis.

Results

A total of 46 patients (92 eyes) were studied. Eight patients were women and 38 were men. The mean age was 64.1 ± 10.8 years (range, 37 to 85 years). Coronary artery disease was the indication for surgery in 39 patients. Cardiac valvular disease was the surgical indication in four patients. A combination of coronary artery disease and cardiac valvular disease was the indication in three patients. In addition to heart disease, seven patients had had a myocardial infarction within the previous one month, seven patients had a history of diabetes, 15 patients had history of systemic hypertension, six had cerebrovascular disease, and six had peripheral vascular disease. Preoperatively, patients were using multiple systemic medications including 32 (69%) using calcium channel blockers, 32 (69%) using nitrates, 11 (24%) using beta-blockers, and 11 (24%) using diuretics.

None of the patients had a history of or physical findings consistent with glaucoma. One eye had undergone panretinal photocoagulation for diabetic retinopathy. A retinal tear had been treated in one eye. Four eyes had had cataract extractions. None of the patients were using ocular medications.

The duration of cardiopulmonary bypass ranged from one to four hours (mean, 2.1 hours). Net intravenous fluid balance in the operating room and in the recovery room ranged from a loss of 0.5 liter to a gain of 7.0 liters (mean, 2.9-liter gain). Fluids administered included 0.9% NaCl, lactated Ringers, fresh frozen plasma, platelets, packed red blood cells, and whole blood.

During the study there were no complaints of visual dysfunction. On the first postoperative day patients had gross physical evidence of fluid retention, including swollen hands and fingers, dependent and pitting edema, facial edema, and, occasionally, mild to moderate conjunctival chemosis. All were intubated and artificially ventilated in the surgical intensive care unit. By postoperative day 3 all but two of the patients were extubated and most of the patients had been transferred out of the intensive care unit.

The earliest recorded weight was approximately 40 hours after surgery (Table and Figure). Weight change over this period ranged from a loss of 4 pounds to a gain of 30 pounds with the average being a gain of 9.3 ± 6.7 pounds ($P < .0001$). By postoperative day 3 the average weight change from preoperative examination was a gain of 6.5 ± 5.5 pounds ($P < .0001$).

The mean change in hematocrit (Table and Figure) over the first postoperative day was a

TABLE

COMPARISON OF PRESSURE, WEIGHT, AND HEMATOCRIT CHANGES

TIME	INTRAOCULAR PRESSURE (MM HG)*	P VALUE	WEIGHT (LBS)†	P VALUE	HEMATOCRIT (%)	P VALUE
Preoperative	12.8 ± 3.4		176 ± 30		40.0 ± 5.2	
		.003		<.0001		<.0001
Day 1	14.9 ± 3.7		—		28.8 ± 3.1	
		NS				<.0001
Day 2	13.5 ± 3.0		186 ± 32		27.7 ± 3.3	
		NS		<.0001		<.0001
Day 3	12.5 ± 3.2		184 ± 31		28.4 ± 3.2	

*Earliest postoperative intraocular pressure was measured 15 to 20 hours after surgery.

†Earliest postoperative weight was measured about 40 hours after surgery.

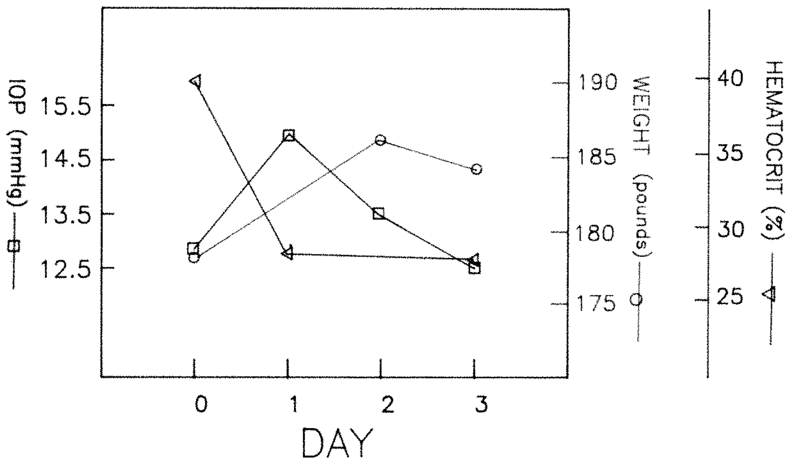

Figure (Deutch and Lewis). Intraocular pressure, weight, and hematocrit on postoperative days 1 to 3 (N = 46).

decrease of 11.3 ± 6.3% ($P < .0001$). On postoperative day 3 the mean change in hematocrit from preoperative level was a drop of 11.6 ± 6.8% ($P < .0001$).

The mean preoperative intraocular pressure was 12.8 ± 3.4 mm Hg (Table and Figure). The first postoperative intraocular pressure measurement was made approximately 15 to 20 hours after surgery. The mean intraocular pressure on the first postoperative day was 14.9 ± 3.7 mm Hg. The change in intraocular pressure between preoperative and postoperative day 1 measurements ranged from a decrease of 5 mm Hg to an increase of 13.5 mm Hg (mean = +2.1 mm Hg, P = .003). Overall, on the first postoperative day, intraocular pressure increased in 29 patients (63%), whereas it decreased in 17 (37%). Thirteen patients (28%) experienced a gain of 5 mm Hg or greater and three patients (7%) had a greater than 10-mm Hg increase in their intraocular pressure. On the second postoperative day the mean intraocular pressure was 13.5 ± 3.1 mm Hg (P = N.S.). By the third postoperative day the mean intraocular pressure had decreased to 12.5 ± 3.2 mm Hg (P = N.S.).

Postoperatively all of the patients received diuretics (usually furosemide), narcotic analgesics, antibiotics (usually cefazolin), and inhaled metaproterenol. Various medications, including antiarrhythmics, benzodiazepines, digoxin, dipyridamole, potassium supplements, noncorticosteroidal anti-inflammatory agents, calcium channel blockers, beta-blockers, and nitroprusside, were administered depending upon clinical status.

Discussion

Ophthalmic complications, principally anterior or posterior ischemic optic neuropathy, have been documented after general surgery.[4-7] This vascular complication may be a result of systemic hypotension, cerebral hypoperfusion, embolic phenomena, or hypothermia. Ophthalmic complications following cardiac bypass surgery have also become an increasing cause for concern. Shaw and associates[1] showed that 25.6% of 312 bypass patients developed neuro-ophthalmic complications while no ocular problems were noted in a control group of 50 patients undergoing major peripheral vascular surgery. Sweeney and associates[2] noted that seven of 7,685 patients developed ischemic optic neuropathy after bypass surgery. As a result of the profound cardiovascular changes that occur during cardiopulmonary bypass, patients undergoing cardiac bypass surgery may be at greater risk.

Vascular events are not the only cause for concern for the bypass patient. Larkin and associates[3] showed that these patients are also at risk for intraoperative increases in intraocular pressure. Within ten minutes of the onset of cardiopulmonary bypass all 24 patients in their study had a rise in intraocular pressure. Their

study found a correlation between intraocular pressure and hemodilution from intravenous infusion needed during the surgery. Their study did not examine the postoperative intraocular pressure dynamics.

In our study intraocular pressure was highest on the first postoperative day. Thereafter intraocular pressure decreased, and by postoperative day 3 intraocular pressure had returned to baseline preoperative levels. It is possible that intraocular pressure was still rising when we measured it on day 1, in which case it is probable that on day 1 intraocular pressure is a close approximation of the peak intraocular pressure. However, it is also possible that intraocular pressure peaked earlier in the postoperative period and was already decreasing by the time of our measurement of intraocular pressure on day 1. We, therefore, do not know when intraocular pressure peaked or the magnitude of the peak.

In our study 29 (63%) of the patients had intraocular pressure increased from baseline on the first postoperative day and in 13 patients (28%) the increase was greater than or equal to 5 mm Hg. Our data extend that of Larkin and associates to show that intraocular pressure rise may persist for 24 to 48 hours after surgery. Thus, a subset of patients appears particularly susceptible to postoperative elevation in intraocular pressure.

Not all investigators have found an intraocular pressure rise after coronary artery bypass surgery. Lilleaasen and Horven[8] did not find an intraocular pressure rise during or after open heart surgery in 12 patients. They suggested this was caused by differences in the composition of the priming solution of the cardiopulmonary bypass equipment and the degree of hemodilution during perfusion. Furthermore, studies of intraocular pressure in uremic patients undergoing hemodialysis did not show pressure rise despite marked changes in osmolality.[9,10] However, the dialysis patient shows a net loss of body weight during dialysis, in contrast to the bypass patient.

Larkin and associates[3] found a significant correlation between intraocular pressure and hemodilution intraoperatively and suggested that hemodilution was responsible for the increased intraocular pressure. In our study marked hemodilution was present throughout the postoperative period. But intraocular pressure, though significantly higher in the initial postoperative period, returned toward baseline levels while the hematocrit lagged behind. Thus, other factors must be brought into account.

Though a significant correlation between intraocular pressure and weight gain was not found in our study, a correlation is suggested (Figure). Because of the critical condition of bypass patients in the early postoperative period, body weight was not measured until almost two days after surgery. Before that time all patients had received strong diuretics. In all likelihood body weight had already declined before our first postoperative weight measurement. A correlation between intraocular pressure and weight gain probably is present earlier in the postoperative period.

In our study one third of the patients did not show an intraocular pressure rise. We suggest two possible explanations for this finding: ocular hypotensive effect of systemic medications and timing of intraocular pressure measurement. Although the preoperative, intraoperative, and postoperative medications and fluids that our patients received were nearly (but not absolutely) identical for each patient, the time course of administration often varied considerably, and the hypotensive effect of systemically administered drugs may be a contributing factor. The confounding factor of the multiple medications that bypass patients receive postoperatively is difficult to consider. Repeated intravenous doses of diuretics, vasoactive substances, narcotics, and sedatives alone or in combination may affect intraocular pressure in ways that are not well understood. It is also possible that more of our patients did experience intraocular pressure increases but our first postoperative intraocular pressure measurement was too late to document it. This is plausible in light of the study by Larkin and associates[3] in which the intraoperative intraocular pressure increases occurred in all patients studied.

The potential clinical implication of these pressure rises is significant when one considers that over 150,000 bypass surgeries are performed in the United States each year.[11] The patient with glaucoma undergoing bypass surgery would appear to have two reasons to be at very high risk for damage to visual function. Not only have these patients been shown to have the greatest increases in intraocular pressure following a fluid load, but their optic nerves have proven to be susceptible to damage from increased pressure.

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OPHTHALMIC MINIATURE

And so, that being done, and my Journal writ, my eyes being very bad, and every day worse and worse, I fear: but I find it most certain that stronge drinks do make my eyes sore, as they have done heretofore always; for, when I was in the country, when my eyes were at the best, their stronge beere would make my eyes sore; so home to supper, and by and by to bed.

—March 28, 1669, Diary of Samuel Pepys

Intractable Diplopia After Vision Restoration in Unilateral Cataract

John A. Pratt-Johnson, F.R.C.S.(C.), and Geraldine Tillson, D.B.O.(T.)

Twenty-four patients lost their ability to fuse when their binocular function was disrupted for at least 2½ years by a unilateral traumatic cataract or a unilateral traumatic cataract followed by uncorrected aphakia. Three patients were 6 years old, one was 8 years old, and the remaining 20 patients were aged 10 years or older at the time of the injury. All patients had intractable diplopia when the cataract was removed and the aphakia corrected. Aniseikonia was not the cause of this inability to fuse and the insertion of an intraocular lens provided no relief. The prognosis for the elimination of diplopia, other than by occlusion of one eye, was poor.

We EXAMINED 24 patients with intractable diplopia following the removal of a traumatic cataract and the restoration of visual acuity to 20/40 or better. These patients have a type of central fusion disruption, having apparently lost their ability to fuse.[1]

Patients and Methods

The 24 patients included in this study were referred between October 1984 and January 1988. None of these patients had been seen by us before the onset of diplopia. Presumably they all had normal binocular function before the traumatic cataract. There was no history of any ocular problems. All patients were symptom free before the injury and reported symptoms attributable to the loss of stereopsis after the injury.

Although the traumatic cataract was removed within one year of its occurrence in 13 of the 24 patients, the optical correction of the resulting aphakia had not always been given immediately or, if prescribed, was not worn consistently. Five of these 13 patients had had an intraocular lens implanted as a secondary procedure many years later.

All 24 patients had traumatic cataracts that were the result of direct injury to the eye only. The injuries were usually of the penetrating type. No head injury or loss of consciousness had occurred. None of these patients were aware of strabismus or any other ocular abnormality before the cataract. The ages of the patients at the time of the injury ranged from 6 to 39 years (average, 18 years). Three were aged 6 years and one was aged 8 years at the time of the trauma; all other patients were over the age of 10 years.

The interval between the development of the cataract and the restoration of the best possible visual acuity to that eye ranged from 2½ to 40 years (average, 14 years). Eight patients had received an intraocular lens. Sixteen patients had been fitted with a contact lens before our examination and wore the lens for all tests.

All patients underwent a detailed orthoptic examination, with particular emphasis on fusional ability.

Results

The patients typically complained of constant double vision when the aphakia was corrected either by an intraocular lens or with a contact lens. Some patients who wore a contact lens were also aware of the diplopia when the con-

Accepted for publication Sept. 21, 1988.
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tact lens was removed. Detailed questioning elicited that the second image was always "bobbing up and down." This was the most distressing factor for the patients. The bobbing of an image was not present when either eye was occluded. Bobbing typically occurs in central fusion disruption from other causes.

Best-corrected visual acuity ranged from 20/40 to 20/20 in the affected eye and 20/30 to 20/15 in the unaffected eye. The affected eye in all patients was exotropic, hypotropic, and excyclotropic. During testing the deviation varied constantly, particularly vertically, although the patients did not change fixation. In all cases the strabismus had apparently developed secondary to the cataract or during the time that the aphakia was uncorrected. Surgical realignment did not help these patients regain fusion but made the diplopia more troublesome because of the proximity of the second image to the real one.

Sensory testing showed that all patients had central fusion disruption and were unable to superimpose any type of slide on a haploscopic device, such as a synoptophore, except for momentarily, because the image seen by the aphakic eye kept bobbing. Patients also characteristically described the same bobbing phenomenon when an attempt was made to join the images with prisms in free space.

These patients were also tested for aniseikonia. Because the American Optical Eikonometer can only be used with patients who have fusion and stereopsis, it was not used with our patients. All patients were asked to compare the size of the diplopic images of a target 6 meters away. They were also asked if they noticed any difference in image sizes when they attempted to superimpose synoptophore slides. The Awaya New Aniseikonia Tests were used to test 18 patients. These patients were able to detect differences as small as 1% (range, 0% to 10%; average, 2%). Aniseikonia did not seem to be the cause of the inability to fuse in these patients.

Aniseikonia was no greater subjectively in the patients fitted with a contact lens than in those with an intraocular lens. Subjective aniseikonia was not a problem for our patients. Aniseikonia was also measured with the Awaya New Aniseikonia Tests in 15 different patients who had had a unilateral nontraumatic cataract removed and the resulting aphakia corrected with a contact lens or an intraocular lens but who had retained their ability to fuse. A similar range of aniseikonia was found in this second group of patients.

Discussion

It is generally assumed that if fusion is developed in childhood and maintained until visual maturity is reached, the ability to fuse cannot be lost. It is also thought that if fusion is disrupted later in life, it can be regained once good visual acuity and ocular alignment are reestablished, even after an interval of several years. However, this is not always the case. We found central fusion disruption following sensory deprivation of more than 2½ years' duration.

Although diplopia probably does not occur in a large number of patients with traumatic cataract, it is nevertheless a serious problem for the patients in whom it does occur. The symptoms in this group of patients with unilateral traumatic cataract are identical to and just as distressing as those occurring in patients who have developed a central fusion disruption from head injury.[2]

We are unable to judge the incidence or frequency of this problem since we do not routinely see adult patients who wish to have their cataracts treated. We have seen only those adult patients who developed diplopia after extraction of a traumatic cataract and who were referred to us by their ophthalmologist for consultation.

The prognosis for regaining fusion is unknown in these cases. There are many problems associated with trying to restore fusion. In addition to an intraocular lens or contact lens, a full optical correction for near and distance of any residual refractive error must be worn to get the best possible visual acuity. The absence of accommodation on the side of the aphakic or pseudophakic eye must be treated with a bifocal spectacle lens. Adjustable suture strabismus surgery followed by prismatic neutralization of any residual deviation must be used to eliminate the strabismus. The aim of treatment is to maintain superimposition of the images in an effort to retrain the fusion ability. The resultant effects of this superimposition, one of which is bobbing, are not only uncomfortable and inconvenient for most patients but may be dangerous. The patient cannot accept this type of treatment when at work, driving, or

taking part in recreational pursuits where diplopia would be hazardous.

It is not surprising, therefore, that patients become discouraged and give up trying to regain fusion, preferring to occlude one eye or to remove their contact lens.

Although many people would consider that visual maturity is reached by the age of 6 years, it is perhaps more generally accepted that visual maturity is obtained by the age of 10 years. In this study, the clinical findings in the four patients who were less than 10 years old when the injury occurred were the same as those in the 20 patients who were over 10 years of age.

Jain, Mohan, and Gupta[3] described 28 children below the age of 10 years with unilateral traumatic cataract who were fitted with a hard contact lens after removal of the cataract. The recovery of binocular function was more frequent if the patients were over the age of 7 years at the time of injury and in those patients in whom the removal of the traumatic cataract and the contact lens correction of the aphakia occurred within eight months of trauma. This finding of a higher incidence of recovery of binocular function in patients whose binocular function was disrupted for less than eight months is compatible with the findings in our study.

The important factor in our study seems to be the interval over which the patients were unable to fuse, either because of the cataract itself or because of the cataract combined with a long period of uncorrected aphakia after cataract extraction. This interval ranged from 2½ to 40 years.

Our 24 patients developed secondary strabismus approximately one year or longer after the injury. This appears to be an indication of intractable diplopia after the restoration of good vision to the affected eye. Many patients noticed some diplopia even with the aphakia uncorrected. It must be emphasized that surgical realignment of the eyes did not eliminate the diplopia.

The bobbing of the image seen by the affected eye did not vary with the type of optical correction. It was not attributable to any particular type or make of intraocular lens, to an ill-fitting contact lens, or to the wearing of a uniocular aphakic spectacle.

Aniseikonia did not prevent the restoration of fusion in this group of patients. Many patients with unilateral aphakia can adapt to aniseikonia of a much larger amount than that recorded in this study.[4]

Difficulty in restoring fusion to some patients who had had a unilateral cataract removed, particularly a traumatic cataract, and a contact lens fitted to that eye was reported over 30 years ago.[5-8] These reports emphasized the significance of the interval over which fusion was prevented when giving a prognosis for the restoration of binocular single vision in patients with any type of unilateral cataract, but especially the traumatic type. It was suggested that any patient with a long-standing unilateral cataract or with prolonged uncorrected unilateral aphakia should undergo an orthoptic examination before attempts to reestablish binocular single vision were made. These studies included some cases of loss of fusion occurring after unilateral nontraumatic cataract. Since our study was completed, we have also seen a patient who had developed a nontraumatic unilateral cataract and appears to have lost his ability to fuse. He was 38 years old and had the cataract removed ten years after its diagnosis. He has been aware of intractable diplopia ever since being fitted with a contact lens two months after the cataract extraction. The signs and symptoms in this patient were the same as those occurring in the 24 patients in our study.

In 1986 Kushner[9] reported five cases of intractable diplopia after treatment of unilateral cataract. Three of his patients were children, with disruption of fusion following the presence of a unilateral traumatic cataract for several years. Kushner referred to this as horror fusionis. Cases of binocular diplopia with no fusion ability have also been described as horror fusionis.[10-12] We, however, found the literature about horror fusionis confusing, and prefer to use the term central fusion disruption when referring to acquired intractable binocular diplopia occurring in visually mature adult patients.

Hamed, Helveston, and Ellis[13] described patients with persistent binocular diplopia after cataract surgery. Although this study included diplopia from many different causes, some of the cases may have been the result of central fusion disruption associated with prolonged sensory deprivation of the affected eye from the cataract.

Those patients in whom it is proposed to remove a long-standing unilateral traumatic cataract and insert an intraocular lens need to be informed of the possibility of intractable

diplopia. Unfortunately, the vision is usually so poor before the extraction that the potential binocular function of the patient cannot be assessed.

The possibility of intractable diplopia should be discussed with patients who have had their fusion interrupted by the presence of a traumatic cataract or by uncorrected aphakia for more than two years. This may argue for initial contact lens correction of the aphakia and secondary, rather than primary, intraocular lens correction once the patient's fusion status has been assessed. An orthoptic evaluation should be obtained with the patient wearing the appropriate contact lens.

Substituting an intraocular lens for a contact lens in patients who are already aphakic and have the type of central fusion disruption described herein will not affect the intractable diplopia. The intractable diplopia will not only persist, but it will be unavoidable except by occluding an eye. Patients with a contact lens can often obtain marked relief by simply removing the contact lens, thus blurring the image seen by the aphakic eye or even enabling them to ignore it altogether.

The presence of a secondary strabismus may be an indication of central fusion disruption. Elimination of the strabismus, if the patient has lost the ability to fuse, will only emphasize the diplopia because the second image will be closer to the real one.

Treatment intended to restore fusion in patients with intractable diplopia is extremely inconvenient and difficult for the patient and the prognosis is largely unknown. Therefore, this emphasizes the need for prophylactic removal of a unilateral opaque traumatic cataract with immediate and continued optical correction of the resulting aphakia as soon as the cataract starts to prevent fusion.

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Contact Lens-Related Deep Stromal Neovascularization

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We observed five eyes (five patients) with deep stromal neovascularization and scarring in patients wearing soft contact lenses during a six-month period. There was no evidence suggestive of other causes of interstitial keratitis. Two patients were aphakic and required a penetrating keratoplasty. Deep stromal vascularization must be added to the growing list of visually significant soft contact lens complications, and soft lens wear should be considered in the differential diagnosis of deep stromal neovascularization.

SOFT CONTACT LENSES have been associated with many complications. In most cases the problems are minor and reversible.[1-4] Vision-threatening complications include corneal ulcers and extensive superficial vascularization resulting in central corneal scarring. Contact lens-induced keratopathy is associated with central superficial corneal vascularization and scarring attributed to chemical hypersensitivity.[5] Deep corneal vascularization and scarring has been reported in aphakic and cosmetic contact lens wearers, but has been a benign peripheral disease not associated with significant loss of visual acuity.[6-8]

Our five patients, soft contact lens wearers seen over the course of six months, had deep corneal vascularization just anterior to Descemet's membrane. The vascularization was associated with deep corneal infiltration, lipid deposition, and scarring. In two patients, corneal transplantation was necessary because of permanent, marked central corneal scarring and decreased vision.

Accepted for publication Oct. 4, 1988.

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Subjects and Methods

We reviewed the outpatient records of all soft contact lens wearers with deep corneal vascularization examined during the six-month period from August 1984 to February 1985. Information was obtained from the records and the patients concerning previous ocular problems, type of contact lens worn, method of lens disinfection, history of lens wear, and follow-up care (Table). Careful slit-lamp examinations were performed in all cases. All but one patient had an intermediate strength purified protein derivative test for tuberculosis and a fluorescent treponemal antibody absorption (FTA-ABS) test for syphilis. In eyes requiring corneal transplantation, histopathologic specimens were stained with hematoxylin and eosin, periodic acid-Schiff, and oil red O.

Case 1

A 63-year-old monocular aphakic man had redness and light sensitivity in his left eye for two weeks. He had had an intracapsular cataract extraction and had worn an aphakic extended-wear contact lens continuously for three years. The lens had been comfortable and problem free. The patient's medical history was significant for insulin-dependent diabetes mellitus.

Visual acuity was R.E.: 20/30 and L.E.: hand motions. Moderate conjunctival injection was present. The aphakic contact lens moved well but had multiple surface deposits. The corneal epithelium was intact. There was diffuse superficial and deep corneal neovascularization associated with three large, dense, white deep stromal infiltrates. The vessels were not emanating from the cataract wound (Fig. 1, left). The

TABLE
SUMMARY OF CASES

	CASE 1	CASE 2	CASE 3	CASE 4	CASE 5
Visual acuity	R.E.: HM L.E.: 20/100*	R.E.: 20/30	R.E.: 20/200 L.E.: 20/40	R.E.: 20/40	R.E.: 20/20 L.E.: 20/20
Symptoms	Visual loss, photophobia	Photophobia	Visual loss	Visual loss	None
Aphakic or cosmetic	Aphakic	Cosmetic	Aphakic	Cosmetic	Cosmetic
Daily- or extended-wear	Extended-wear	Extended-wear	Daily-wear	Daily-wear	Daily-wear
Exposure to preservatives	Not present	Mild	Mild	Mild	Mild
Tight fit	Not present	Not present	Not present	Not present	Mild
Conjunctival inflammation	Severe	Moderate	Not present	Not present	Not present
Area of deep vessels (deg)	360	360	360	90	90
Results of FTA-ABS, purified protein derivative	Negative	Not done	Negative	Negative	Negative

*Visual acuity was HM (hand motions) initially and improved to 20/100.

contact lens was removed and cultured on blood agar media. No growth was noted.

Contact lens use was discontinued and the patient was treated with prednisolone acetate 1% four times daily, topical antibiotics, and cycloplegic eyedrops. The conjunctival hyperemia resolved. Topical medications were tapered and discontinued over several months. Best-corrected visual acuity improved to 20/100 after three months and remained at this level because of deep central scarring (Fig. 1, right). Ten months after the initial examination, the patient underwent a penetrating keratoplasty and secondary intraocular lens implantation for visual rehabilitation.

Histopathologic findings—Corneal sections demonstrated an intact epithelium and Bowman's layer. The superficial stroma was unremarkable. The mid and deep stroma contained many blood vessels, some longitudinal and some in cross-section, with red blood cells in the lumen of some of the larger vessels (Fig. 2, top). There was an accompanying chronic inflammatory cell infiltrate in the same area. Frozen sections stained with oil red O demonstrated lipid droplets in the deeper stroma (Fig. 2, bottom) close to the area of neovascularization. Descemet's membrane was intact and did not show any significant change.

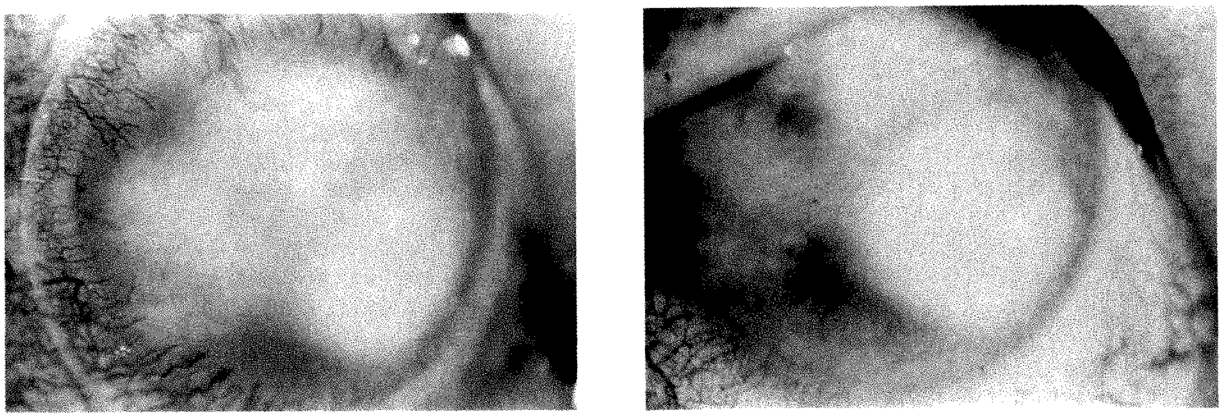

Fig. 1 (Rozenman and associates). Case 1. Left, At time of initial examination with aphakic extended-wear lens in place. Marked conjunctival injection, deep stromal vascularization, and three large stromal infiltrates are present. Right, Three months after discontinuing lens wear and after institution of topical corticosteroid therapy. The eye is not inflamed, but large deep corneal scars are present.

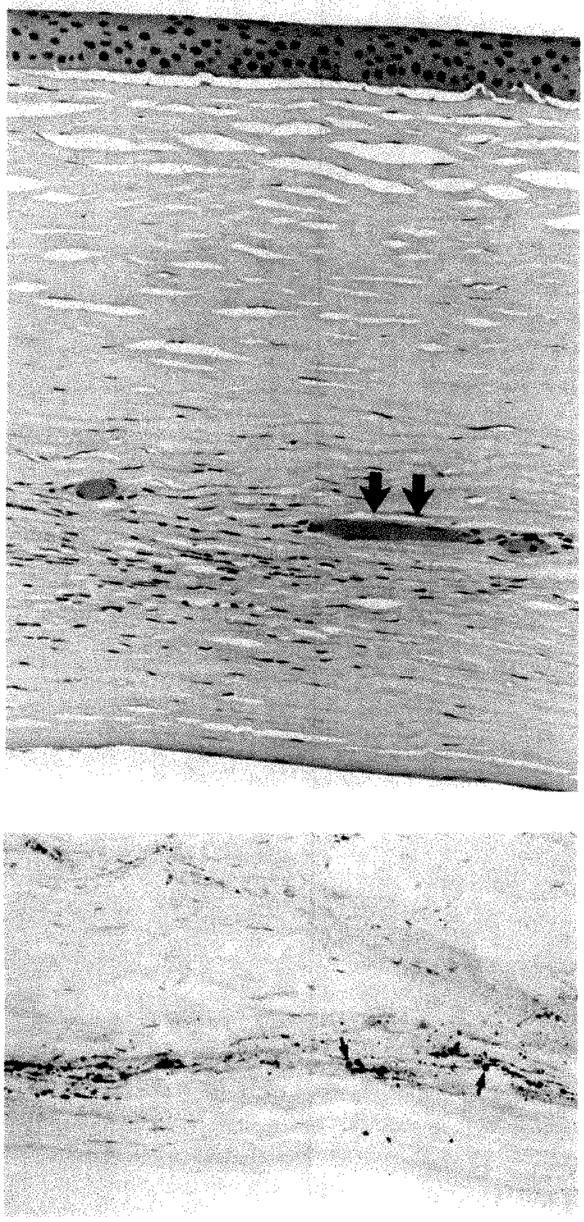

Fig. 2 (Rozenman and associates). Case 1. Top, Deep corneal stromal neovascularization (arrows) with chronic inflammatory cell infiltrate (hematoxylin and eosin, ×200). Bottom, Fat globules in deep corneal stroma (arrows) (oil red O, ×200).

Case 2

A 22-year-old man who wore a cosmetic extended-wear lens in his right eye complained of redness and irritation in the right eye for one month. The patient had removed his lens and used heat disinfection once a week. On examination, visual acuity was R.E.: 20/30 with the contact lens and L.E.: 20/20 with spectacle correction. Moderate conjunctival injection and giant papillary conjunctivitis were present in the right eye, and the corneal epithelium was intact. The lens moved well. There were peripheral superficial and deep stromal vessels associated with three white stromal infiltrates extending toward the visual axis. Contact lens use was discontinued and the patient was treated with prednisolone acetate 1% eyedrops four times daily and topical antibiotics. After one month, the infiltrates were slightly smaller and the stromal vessels appeared less active. The patient was lost to follow-up.

Case 3

A 58-year-old man with a five-year history of aphakic daily-wear soft contact lens use was referred because of bilateral corneal opacities and decreased vision of two months' duration. The patient removed his lenses daily and had used heat sterilization once a week. Visual acuity with contact lenses was R.E.: 20/200 and L.E.: 20/40. The conjunctiva was normal and the contact lenses fit and moved well in both eyes. The corneal epithelium was intact. There was diffuse superficial and deep stromal neovascularization. The deep vessels extended into the visual axis and were associated with disk-like opacities anterior to Descemet's membrane in both eyes (Fig. 3).

Contact lens use was discontinued and the patient was treated with prednisolone acetate 1% eyedrops four times daily in both eyes. The stromal opacities and visual acuity remained unchanged. The patient underwent a penetrating keratoplasty in the right eye three months later.

Histopathologic findings—The corneal specimen showed irregular thickening of the epithelium with basal cell edema. Bowman's membrane was intact. A few blood vessels were observed in the superficial stroma, but new blood vessels were primarily noted just next to Descemet's membrane in the deeper central stroma. Chronic inflammatory cells were also noted in this area (Fig. 4, top). Descemet's membrane was intact. Fat stains demonstrated fat droplets in the deeper stroma (Fig. 4, bottom). The endothelial cells were few in number and appeared flattened.

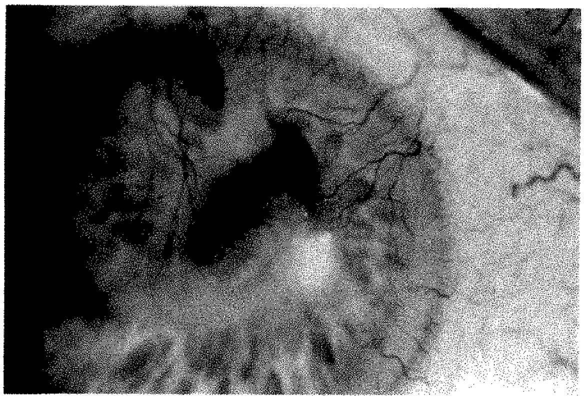

Fig. 3 (Rozenman and associates). Case 3. Deep corneal vascularization and a central disciform opacity and lipid infiltrate are present.

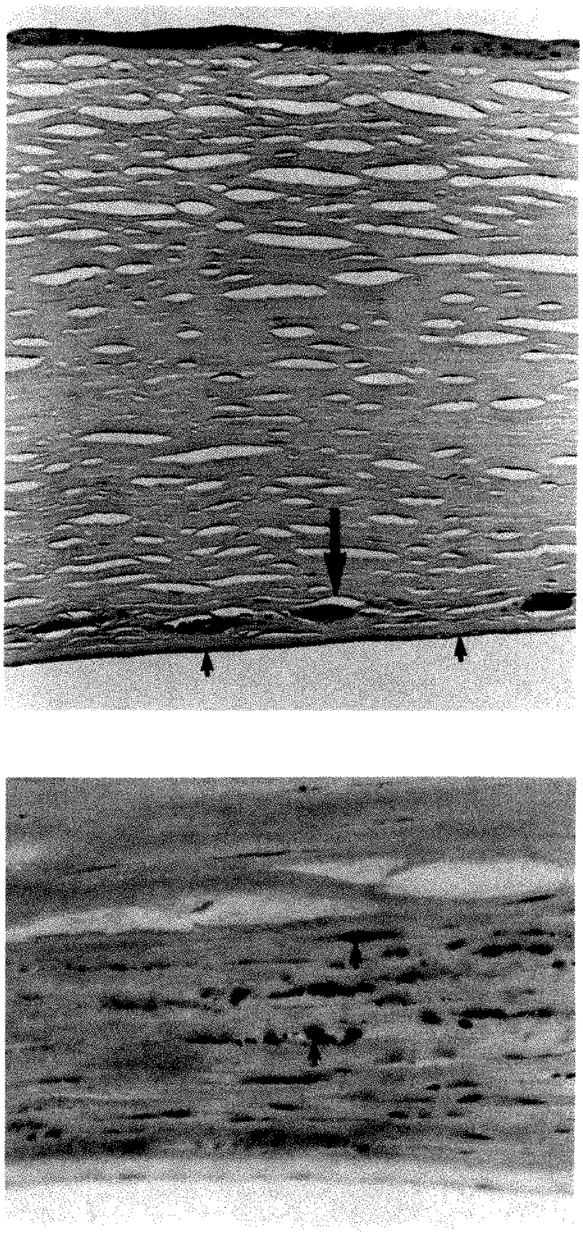

Fig. 4 (Rozenman and associates). Top, Blood vessels in deep stroma (big arrow) close to Descemet's membrane (small arrows) (hematoxylin and eosin, ×200). Bottom, Fat globules in deep stroma (arrows) (oil red O, ×400).

Case 4

A 25-year-old man who had worn cosmetic daily-wear soft lenses for two years complained of blurred vision in the right eye for one week. The patient used chemical disinfection every other day.

On examination, visual acuity with contact lenses was R.E.: 20/40 and L.E.: 20/30. The conjunctiva was normal and the lenses moved well. The epithelium was intact. There was a sector of superficial and deep stromal corneal neovascularization in the right eye that extended toward the pupil and was surrounded by a white deep stromal opacity (Fig. 5).

Contact lens wear was discontinued and the patient was given topical corticosteroids. There was no change in the stromal opacity during a follow-up period of four months.

Case 5

A 35-year-old woman who had worn cosmetic daily-wear soft contact lenses for two years had a white spot on her right cornea. She had no symptoms. The patient used daily chemical disinfection.

On examination, visual acuity was 20/20 in both eyes. The conjunctiva appeared normal. The contact lenses were clean but did not move on blinking. The epithelium was intact. There was deep peripheral stromal vascularization associated with deep opacities temporally in both eyes. The scars have remained stable over a five-month period despite corticosteroid therapy.

Discussion

Although peripheral superficial vascularization is a relatively common, nonvision-threatening complication of contact lens wear,

Fig. 5 (Rozenman and associates). Case 4. Quiet eye with sector of deep stromal vascularization surrounded by an apparent lipid infiltrate.

corneal neovascularization associated with central corneal scarring is uncommon.[6,9,10] Bloomfield, Jakobiec, and Theodore[5] reported central corneal pannus in a soft contact lens patient with a history of prolonged chemical hypersensitivity reaction. Aphakic and cosmetic soft contact lens patients have been documented to develop deep corneal neovascularization and stromal opacities.[6-8] These opacities have improved after lens discontinuation and did not significantly reduce vision.[6-8] In two of our five patients with deep stromal vessels, permanent corneal opacities involving the visual axis necessitated penetrating keratoplasty for visual rehabilitation. There was no history of herpes simplex keratitis, tuberculosis, or syphilis in our patients. None of the patients demonstrated a significant epithelial break or physical findings consistent with infectious keratitis. For this reason, cultures and sensitivity tests were not performed.

Hypoxia, inflammation, and corneal edema are associated with corneal neovascularization. Patients who use extended-wear soft contact lenses frequently develop small amounts of peripheral superficial vascularization that are attributed to hypoxia. Patients with poorly fit standard hard lenses without sufficient movement to ensure adequate tear exchange and oxygen delivery under the lens are also prone to develop superficial and deep vascularization. One can speculate that deep vessels may reflect a more severe or prolonged hypoxic insult compared to superficial vessels. Inflammation is a factor in corneal neovascularization seen in prolonged chemical hypersensitivity reactions and more frequently in conditions unrelated to the use of contact lenses, including herpes simplex keratitis, syphilitic interstitial keratitis, and Cogan's syndrome.

It is difficult to determine the cause of the deep vessels in this series of patients. Our patients were heterogeneous with regard to the type of lens worn, exposure to preservatives, lens fit, and the presence of inflammation (Table). Deep stromal vascularization was seen in aphakic patients as well as those who wore cosmetic, daily-wear, and extended-wear lenses. All but one patient used solutions containing preservatives for lens disinfection. The patient with the most severe corneal infiltrates (Case 1) had no history of chemical exposure since the lens had not been removed for three years. The prolonged use of an extended-wear lens in this patient suggests that hypoxia may be a significant factor. Only one patient in the group had an obviously tight fitting lens (Case 4). Extended-wear lenses are associated with hypoxia when the eyes are closed despite optimal fitting characteristics. Two of the patients, however, used well fitting daily-wear lenses that should not be associated with significant hypoxia. Conjunctival inflammation and symptoms associated with ocular inflammation were present in only two patients (Cases 1 and 2). These patients with an active inflammatory component to their problem responded partially to topical corticosteroid therapy, in contrast to the patients without inflammation who did not improve after discontinuation of the lenses. The development of deep neovascularization may have a multifactorial origin and simply reflect the severity of a variety of insults.

Deep stromal vascularization and corneal scarring is a serious lens complication that may cause permanent loss of vision when the visual axis is involved. As in other conditions associated with deep vessels, inflammatory and lipid infiltrates are present in the acute stage and permanent scarring results. Deep vessels and infiltrates develop insidiously and progress in the absence of acute symptoms. Severe visual loss occurred before two of the patients sought medical care. Routine follow-up care of soft contact lens wearers is important to detect this complication before the visual axis is involved. Cosmetic contact lens wear should be discontinued in patients who develop deep corneal neovascularization.

Patients wearing contact lenses for visual rehabilitation may also develop deep corneal

neovascularization. Minimal peripheral neovascularization may be treated by changing from extended-wear to daily-wear contact lenses. Attention should be paid to obtaining optimum lens fit. An attempt should also be made to switch the patient to high-oxygen permeability lenses. Regardless, these patients should be followed up carefully. When neovascularization continues in aphakic patients despite these changes, a secondary intraocular lens implantation or corneal remodeling surgery should be considered for visual rehabilitation. Contact lens-associated deep stromal neovascularization is a visually threatening disease that reinforces the need for contact lens wearers to obtain periodic follow-up examinations.

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Nd:YAG Laser Photodisruption of Hemorrhagic Detachment of the Internal Limiting Membrane

V.-P. Gabel, M.D., Reginald Birngruber, Ph.D., H. Gunther-Koszka, M.D., and Carmen A. Puliafito, M.D.

We used a Q-switched Nd:YAG laser to create an opening in the internal limiting membrane in three eyes with hemorrhagic detachment of the internal limiting membrane. In all instances, after membranotomy blood was rapidly cleared from the preretinal space resulting in prompt improvement in visual acuity. No retinal injury was observed. Nd:YAG laser photodisruption may be useful in the treatment of some cases of subinternal limiting hemorrhages.

HEMORRHAGIC DETACHMENT of the internal limiting membrane may occur after retinal vessel rupture associated with physical exertion and increased venous pressure (Valsalva retinopathy) or in retinal vascular disorders, such as proliferative diabetic retinopathy.[1] Visual acuity is often profoundly reduced. Spontaneous clearing of the hemorrhage usually occurs, but may take several months.[2,3] We used Nd:YAG laser photodisruption to create a focal opening in the internal limiting membrane in eyes with premacular subinternal limiting membrane hemorrhage, permitting the preretinal blood to enter the vitreous cavity where it is resorbed more rapidly. In each eye, vision improved dramatically within seven days. No retinal injury from the laser photodisruption was observed. This treatment technique may be useful in treating selected cases of hemorrhagic detachment of the internal limiting membrane, particularly when rapid restoration of normal visual function is indicated.

Accepted for publication Aug. 10, 1988.

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Case Reports

Case 1

Two weeks before examination, this 25-year-old man developed sudden loss of vision in his left eye after physical exertion during military training. Results of examination of the right eye were normal. Visual acuity in the left eye was counting fingers at 1 foot. Ophthalmoscopy showed a circumscribed round dark red mass with a convex surface covering the left macula (Fig. 1, top left). The anterior surface of the hematoma (the internal limiting membrane) was opened by two Nd:YAG laser pulses (3.6 mJ, fundamental mode) at the inferior margin of the lesion.[4] Blood immediately flowed through the membranotomy and dispersed into the inferior vitreous. One hour after treatment (Fig. 1, top right), the subhyaloid hemorrhage had substantially cleared, resulting in immediate subjective improvement in vision. Three days after treatment, a small amount of hemorrhage was present below the detachment of the internal limiting membrane (Fig. 1, bottom left). Eight days after treatment (Fig. 1, bottom right), visual acuity was 20/25 without correction. A small inferior vitreous hemorrhage was seen. The retina underlying the site of the membranotomy was normal in appearance.

Case 2

A 55-year-old woman experienced sudden visual loss in her left eye four days before

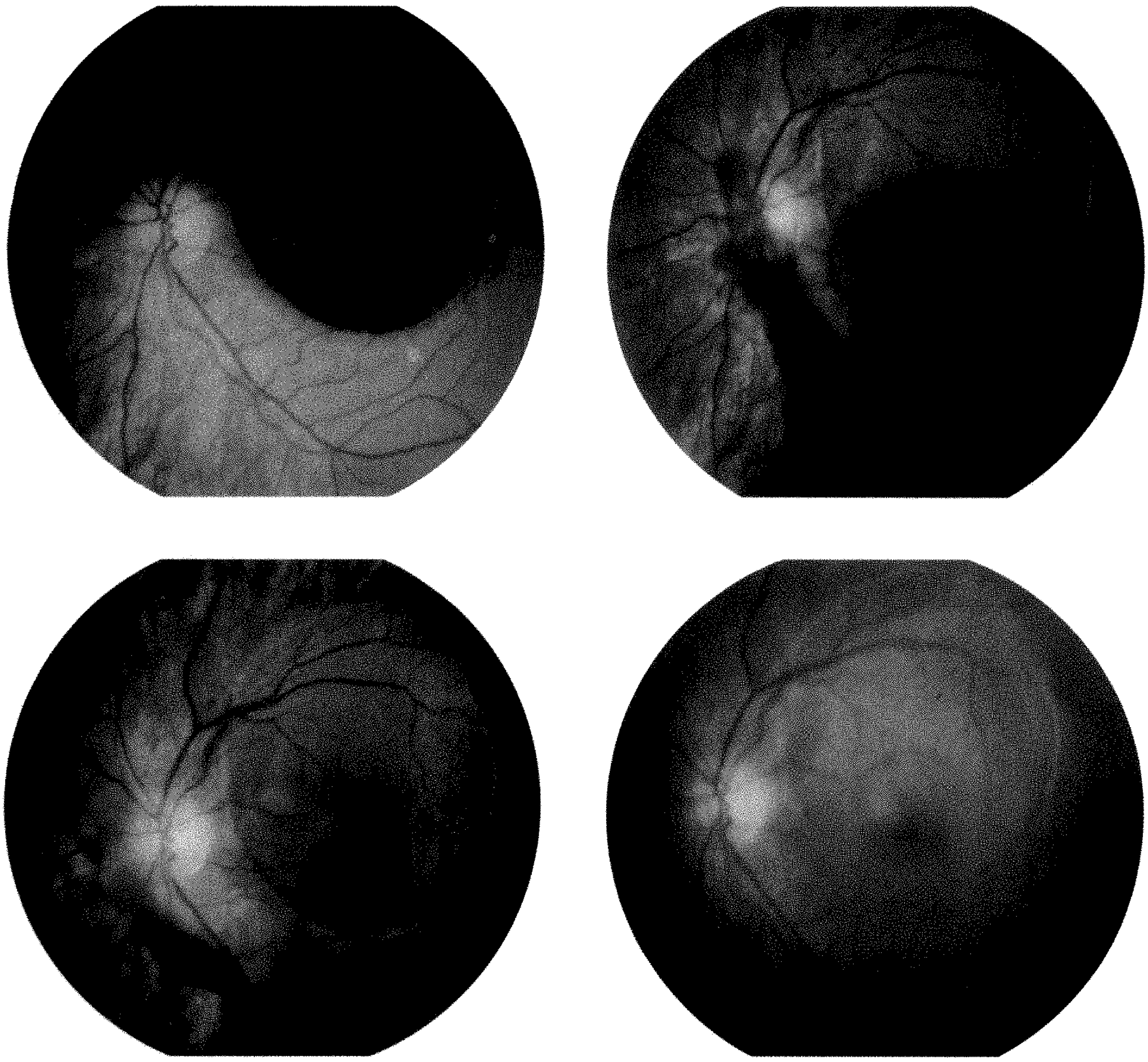

Fig. 1 (Gabel and associates). Case 1. Top left, Preoperative fundus appearance. Note large subinternal limiting membrane hemorrhage in the macula. Top right, One hour after Nd:YAG laser opening of the internal limiting membrane, the preretinal hematoma is much smaller in size. Note egress of blood into the inferior vitreous. Bottom left, Fundus appearance three days after treatment. Only a small amount of blood is left in the detachment cavity. Bottom right, Fundus appearance one week after treatment. The hemorrhage has completely cleared and a shallow serous detachment of the internal limiting membrane remains.

examination. Results of examination of the right eye were normal. In the left eye, visual acuity was hand motions and hemorrhagic detachment of internal limiting membrane was seen in the macula. The blood within the detachment cavity had partly settled, but the fovea was covered by hemorrhage (Fig. 2, left). Scattered preretinal hemorrhages were seen adjacent to the disk and the superior vascular arcade. Perforation of the internal limiting membrane was performed using five laser pulses of 15 to 25 mJ each. Immediately after treat-

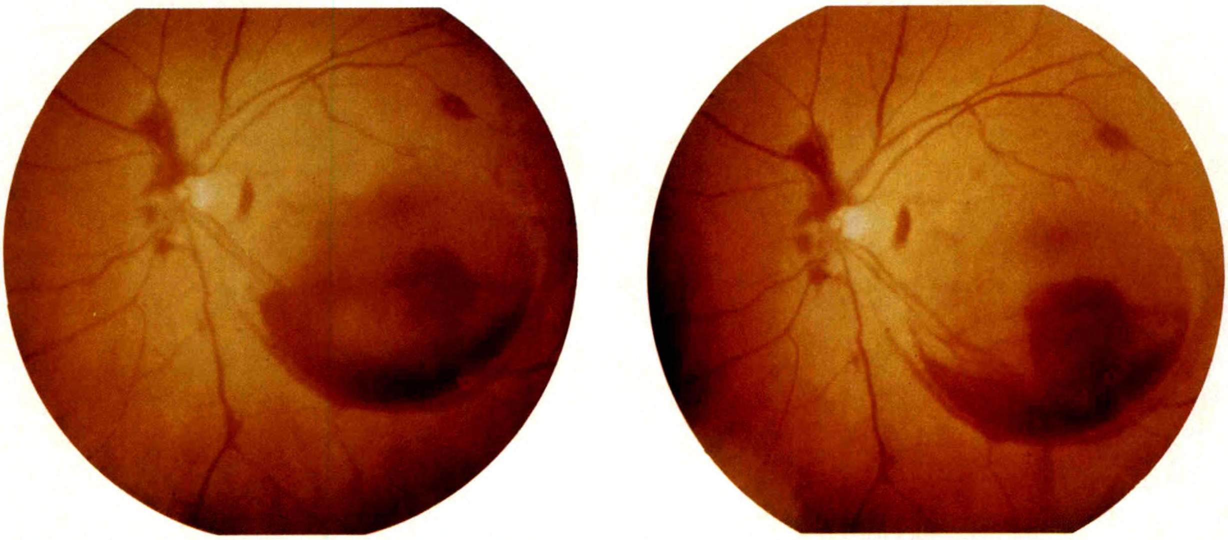

Fig. 2 (Gabel and associates). Case 2. Left, Preoperative fundus appearance. Note hemorrhagic detachment of the internal limiting membrane and hemorrhage covering the fovea. Right, One hour after Nd:YAG laser treatment. The preretinal hemorrhage has partially drained and the hemorrhage in front of the fovea has cleared.

ment, a stream of blood flowed into the inferior vitreous. Within one hour after treatment, the blood had cleared from the fovea (Fig. 2, right). No retinal injury was observed. Three days after treatment, a mild vitreous hemorrhage was noted, which spontaneously cleared. Visual acuity six months after treatment was 20/40.

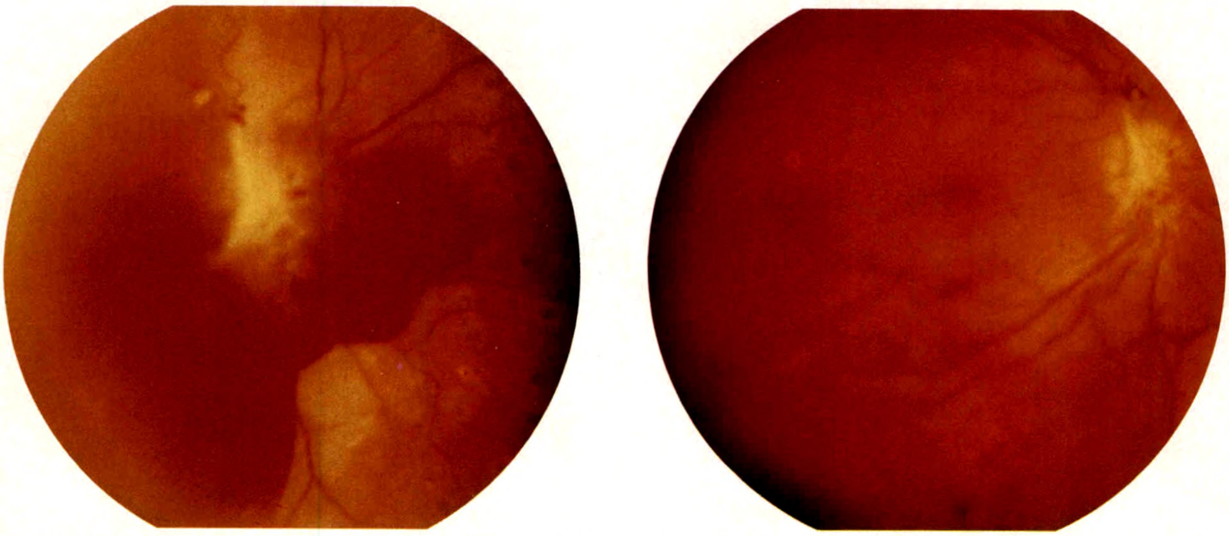

Fig. 3 (Gabel and associates). Case 3. Left, Preoperative fundus appearance showing subinternal limiting membrane/subhyaloidal hemorrhage covering the posterior pole. Right, Fundus appearance three days after internal limiting opening. Preretinal hemorrhage has cleared from premacular space and settled into the inferior vitreous.

Case 3

A 48-year-old man with diabetic proliferative retinopathy developed sudden loss of vision in his right eye. The left eye had long-standing poor vision because of a traction detachment of the macula. Visual acuity was R.E.: counting fingers at 1 foot. Ophthalmoscopy demonstrated a large subinternal limiting membrane hemorrhage covering the posterior pole (Fig. 3, left). The hemorrhage was clearly circumscribed inferiorly, was convex in contour, and covered the macula. The internal limiting membrane was perforated using five single Nd:YAG laser pulses of increasing energy from 12 to 50 mJ. The fifth pulse at a higher energy level was necessary since four pulses at a lower energy level were not sufficient to open the internal limiting membrane. Two days later (Fig. 3, right), the hemorrhage in the macula had cleared and visual acuity was 20/40. The retina in the area of laser treatment appeared to be normal.

Discussion

Nd:YAG laser photodisruption is commonly used for a variety of anterior segment procedures, in particular posterior capsulotomy and iridotomy.[5] Posterior segment applications of the Nd:YAG laser have generally been limited to transection of vitreous membranes in selected cases of diabetic traction retinal detachment, sickle cell retinopathy, and complicated retinal detachment.[6-9] Widespread application of Nd:YAG laser photodisruption for the treatment of posterior segment conditions has been limited because of the extent and complexity of membranes found in proliferative retinopathies (requiring hundreds or even thousands of laser pulses); the frequent presence of concomitant media opacity, such as vitreous hemorrhage, limiting photodisruption; the presence of vascularized membranes that bleed following photodisruption; the possibility of severe complications, such as retinal or choroidal hemorrhage or retinal hole formation; and the lack of an optimal delivery system for intravitreal use.[10]

Perforation of the internal limiting membrane was readily achieved, although the laser pulse energy necessary varied from 3.6 to 50 mJ. As with other Nd:YAG laser procedures, low pulse energies were used initially and then increased as necessary to achieve the desired clinical effect. In Case 3, a pulse energy of 50 mJ was used only after less energetic pulses failed to create an opening. We treated the inferior aspect of the detachment cavity, away from the fovea. No retinal injury was observed in any of our patients. We speculate that the preretinal blood shields the underlying retina from laser-induced injury, even at the high pulse energies used in two of our patients. This technique may be difficult to use in eyes with less extensive hemorrhage than that seen in our patients. Argon and xenon arc photocoagulators have been used to rupture the internal limiting membrane in such eyes, but their use appears to be more difficult than our approach and carries with it the additional risk of photocoagulation injury to the underlying retina (even through the preretinal hemorrhage).[11-13]

Nd:YAG laser photodisruption significantly accelerated the recovery of visual acuity in our patients. Although visual acuity in patients with exertional or Valsalva retinopathy usually returns to normal, clearing of the subretinal hemorrhage may take months. Conservative management of such cases certainly can be justified. However, Nd:YAG laser therapy provides an additional option that may be valuable in some situations. Nd:YAG laser internal limiting membranotomy may be indicated in cases of persistent or slowly clearing hemorrhage, in patients with an occupational need for prompt restoration of binocular vision, or in patients with poor vision in their fellow eye.

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Ophthalmic miniature

A large part of an editor's job is rejection. Perhaps nine-tenths. In those days at least, it was not only rejection of manuscripts but of those ideas that seemed to come walking into my office every day in the shape of pensive men and women talking with judicious facial expressions about such mutilated concepts as optimist/pessimist, fascist/communist, extrovert/introvert, highbrow/middlebrow/lowbrow; and this claptrap they applied to art, literature and life to the effect that all joy, wit and the pleasures of curiosity were quite squeezed out.

Muriel Spark, *A Far Cry From Kensington*
Boston, Houghton Mifflin Company, 1988, p. 97

Subretinal Hemorrhage in Atrophic Age-Related Macular Degeneration

Fadi Nasrallah, M.D., Alex E. Jalkh, M.D., Clement L. Trempe, M.D., J. Wallace McMeel, M.D., and Charles L. Schepens, M.D.

In eight eyes of eight patients we retrospectively studied the outcome of subretinal hemorrhage occurring in areas of atrophy of retinal pigment epithelium and choriocapillaris secondary to age-related macular degeneration. These patients were followed up for one to 20 months after the initial appearance of the hemorrhage. No subretinal new vessels were associated with these hemorrhages, which resolved over one to 15 months. Our findings indicated that hemorrhages occurring within areas of atrophy are not necessarily associated with subretinal new vessels, and that this type of hemorrhage has a good prognosis for resolution.

Subretinal hemorrhage in eyes with age-related macular degeneration has been strongly associated with the existence of subretinal new vessels. The failure to visualize vessel leakage on fluorescein angiography is usually attributed to blockage of fluorescence by the hemorrhage itself; the leakage usually can be observed when the hemorrhage resolves. In studying subretinal hemorrhage in areas of atrophy secondary to age-related macular degeneration, we found that this type of hemorrhage was not associated with subretinal new vessels and resolved with no complications.

Subjects and Methods

Our study included eight eyes of eight patients who were seen at our institution because of visual symptoms secondary to age-related macular degeneration. The diagnosis was made on the basis of indirect ophthalmoscopy and fluorescein angiography, which showed drusen, areas of atrophy of retinal pigment epithelium and choriocapillaris, or leakage from subretinal new vessels in either eye. The changes in the eyes included in the study were caused predominantly by atrophy of the retinal pigment epithelium and choriocapillaris, and during the initial manifestation or follow-up a subretinal hemorrhage was noted within these areas of atrophy. Three additional eyes with similar findings were excluded from the study because a fibrovascular scar or subretinal new vessels evolved, and we could not determine whether or not the hemorrhages came from the neovascular lesions, despite the fact that the blood was not near the lesions and within an area of atrophy.

We documented the patient's age, sex, involved eye, and visual acuity when the hemorrhage was first observed and when it resolved. Also recorded were the length of follow-up, time needed for absorption of the hemorrhage, other ocular problems, and condition of the fellow eye. The hemorrhages were classified as small if they were less than ½ disk diameter, medium if ½ to 1 disk diameter, and large if more than 1 disk diameter. The spatial relation of the hemorrhage to the fovea was also documented.

Results

Patient ages ranged between 72 and 85 years with a mean of 78.8 years. Two patients were men and six were women. None of the patients was receiving anticoagulative or antithrombotic therapy when the hemorrhage was first observed. One patient reported receiving anti-

Accepted for publication Sept. 30, 1988.
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thrombotic therapy (dipyridamole and acetylsalicylic acid) for cardiac disease before her first examination. Another patient reported erratic intake of acetylsalicylic acid for arthritis before her first examination. Three patients had hypertension controlled by medication; one of these also had a history of cardiac problems. Visual acuity when the hemorrhage was first observed ranged between 20/30 and counting fingers and remained the same in all eyes when the hemorrhage disappeared. The reason for the low visual acuity at the time the hemorrhages were first detected was the atrophic process in all included eyes.

The hemorrhage was small in six eyes, medium in one, and large in one. In no eye was the hemorrhage found in the foveal avascular zone, and no fluorescein evidence of subretinal new vessels associated with these hemorrhages could be identified at any time. The hemorrhages resolved over a one- to 15-month period, and none recurred during follow-up, which ranged from one to 20 months. Hemorrhages occurred bilaterally in one patient during follow-up. The left eye was not included in our study because subretinal new vessels evolved in that eye, and although these were unrelated to the hemorrhage in time and location, we could not determine with certainty whether or not the hemorrhage came from these lesions.

Findings in the contralateral eyes were caused by age-related macular degeneration and were primarily atrophic in six patients, one of whom had developed subretinal new vessels that were treated with photocoagulation. A fibrovascular scar developed in another eye, and still another eye had a retinal pigment epithelial detachment.

The following case report is representative of our eight patients.

Case Report

For a year one patient, an 85-year-old woman, had had reading problems caused by poor vision. Findings from a systemic review and physical examination were unremarkable. At the initial examination, best corrected visual acuity was 20/100 in both eyes. Intraocular pressure was 22 mm Hg in both eyes. Examination of the anterior segment disclosed mild nuclear sclerosis in both eyes. Ophthalmoscopic examination showed multiple drusen in both eyes and well-circumscribed areas of atrophy of retinal pigment epithelium and choriocapillaris around the fovea of both eyes. In the left fundus, there was also a subretinal hemorrhage superonasal to the fovea and overlying an area of atrophy (Fig. 1); a fluorescein angiogram did not show any area of leakage (Fig. 2). Results from an ophthalmic examination one year later were virtually unchanged, except that the subretinal hemorrhage had reabsorbed, exposing an area of atrophy of retinal pigment epithelium and choriocapillaris (Fig. 3).

Discussion

Subretinal new vessels are poorly formed and have weak intracellular junctions that leak profusely.[1] Blood as well as fluorescein dye escape easily through the thin vessel walls and pool in subretinal spaces. Although subretinal new vessels do not always bleed, the finding of an isolated subretinal hemorrhage in a nonmyopic eye has been viewed as highly suggestive for the existence of subretinal new vessels, especially in eyes with age-related changes. Macroaneurysms and choroidal rupture also are causes of subretinal bleeding but were never documented in any of the eyes included in this study. Our study points to other mechanisms by which a subretinal hemorrhage can occur in a nonmyopic eye with age-related macular changes. The hemorrhages occurred within areas of atrophy of the retinal pigment epithelium and choriocapillaris, the latter being a known complication of age-related macular degeneration. The occurrence of subretinal hemorrhages within atrophic areas of choriocapillaris and retinal pigment epithelium is not a newly recognized phenomenon; it has been reported in severely myopic eyes where it was termed "coin lesions."[2] We speculate that the mechanism underlying hemorrhages in severely myopic eyes and in areas of atrophic age-related macular degeneration is similar, although the exact details of bleeding remain speculative. Atrophying areas of choriocapillaris may release blood to the subretinal space. It is possible that the hemorrhages in our study were originally associated with subretinal new vessels, that leakage was blocked by the hemorrhage, and that the new vessels regressed when the hemorrhage resolved, leaving no evi-

Fig. 1 (Nasrallah and associates). Fundus photograph of left eye of 85-year-old patient showing a subretinal hemorrhage (arrow) over an area of atrophy of retinal pigment epithelium and choriocapillaris.

Fig. 3 (Nasrallah and associates). Fundus photograph of same eye as in Figure 1, 12 months later. The subretinal hemorrhage reabsorbed exposing an area of atrophy of retinal pigment epithelium and choriocapillaris (arrow).

dence of leakage. This explanation is unlikely because, first, seven of the eight eyes had hemorrhages too small to block leakage from even small subretinal new vessels, and in the eye that had a large hemorrhage, the reabsorption time was too quick to allow for new vessel regression. In our study the reabsorption time was recorded as one to 15 months, but this end time was when the hemorrhage was first noted to have disappeared and the actual time may have been shorter.

Anticoagulants and antithrombotics may play a role in causing bleeding from subretinal new vessels. In their report, El Baba and associ-

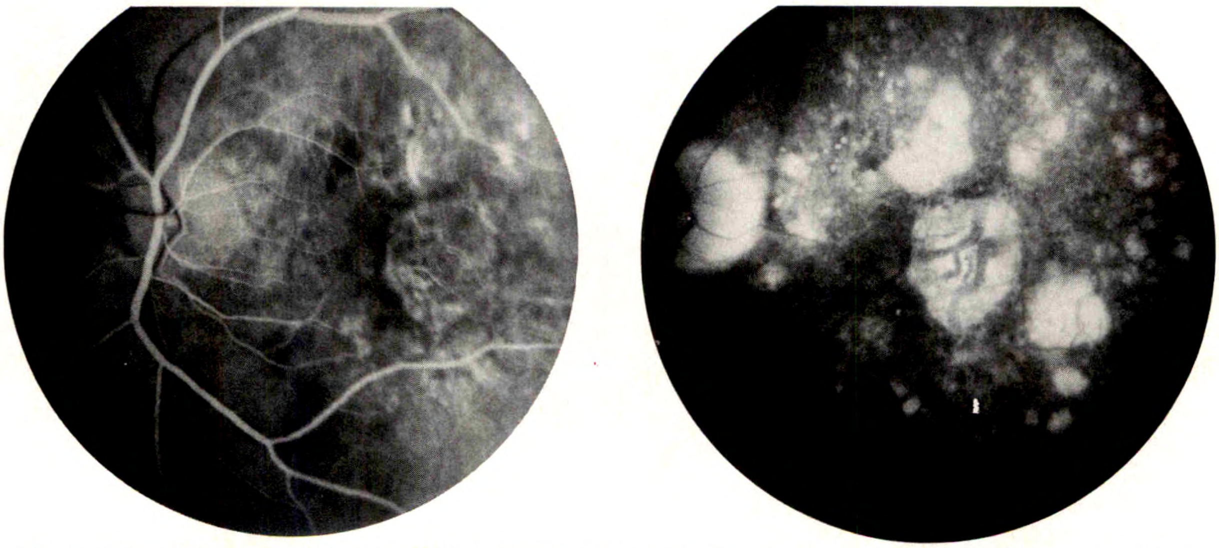

Fig. 2 (Nasrallah and associates). Early (left) and late (right) fluorescein angiography of left eye of patient shown in Figure 1. No evidence of leakage is detected.

ates[3] suggested that anticoagulation may aggravate bleeding from subretinal new vessels producing massive subretinal or vitreous hemorrhages. In our cases the hemorrhages were relatively small, were not associated with subretinal new vessels, and resolved over time. Furthermore, none of our patients was receiving anticoagulative or antithrombotic therapy or had an underlying coagulopathy. It is, therefore, unlikely that impaired coagulation contributed to the subretinal hemorrhages.

Three of the eight patients, or 37.5%, had a history of hypertension or cardiac disease, a percentage comparable to reported figures from epidemiologic studies on the elderly population.[4]

Our study is limited by its retrospective nature and the small number of patients. Larger, prospective studies are needed to evaluate the role of impaired coagulation or other systemic problems in the development of subretinal hemorrhage within areas of atrophy secondary to age-related macular degeneration. We also cannot determine from our study whether subretinal new vessels occur within these areas of atrophy. We have no records of patients with atrophic changes and a subretinal hemorrhage who showed no evidence of fluorescein leakage initially, but showed evidence of subretinal new vessels at follow-up. We also cannot determine whether all subretinal hemorrhages occurring within areas of atrophy secondary to age-related macular degeneration are unassociated with subretinal new vessels. Although most hemorrhages in our study were less than ½ disk diameter, larger hemorrhages also were seen. Thus, size alone cannot serve as an indicator for the presence or absence of subretinal new vessels.

Despite its limitations, our study is unique in that it addresses the problem of subretinal hemorrhage formation in areas of atrophy secondary to age-related macular degeneration and it identifies a different mechanism of subretinal hemorrhage formation in age-related macular degeneration. Our study also stresses the importance of documenting subretinal new vessels before photocoagulation treatment for subretinal hemorrhage in areas of atrophy of the retinal pigment epithelium and choriocapillaris.

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Irregular Astigmatism After Radial and Astigmatic Keratotomy

Peter J. McDonnell, M.D., Patrick J. Caroline, B.A., and James Salz, M.D.

Eleven eyes of six patients, who had been referred for management of irregular astigmatism after receiving crossed incisions for myopic astigmatism, had moderate to marked irregular corneal astigmatism with marked flattening in the meridians of intersecting incisions. All six patients had a decrease in best-corrected visual acuity with spectacles after surgery. Visual acuity with spectacles was 20/40 in five of 11 eyes; with contact lenses it reached 20/40 in ten of 11 eyes. However, two patients could not wear the contact lenses because of lens decentration caused by the marked distortion in corneal topography. Even with contact lenses, visual acuity could only be improved to 20/25 or better in six of 11 eyes.

COMPLICATIONS of combined radial keratotomy and astigmatic keratotomy with intersecting incisions include epithelial inclusions cysts, wound gape, persistent epithelial defects, sterile ulceration, and irregular astigmatism.[1,2] These complications occur whether the incisions for the astigmatism are created at the same time[1] or months after[2] the radial incisions. Because of this accumulating experience, it has been stated that corneal incisions should not intersect.[3] We report a series of 11 eyes with intersecting radial and transverse corneal incisions that resulted in substantial irregular corneal astigmatism.

Patients and Methods

Six patients (11 eyes) were referred for management of irregular astigmatism after combined radial and astigmatic keratotomies. All patients had planned intersecting (crossing) incisions performed at the same time as the radial incisions. One eye also had flagged incisions, with the incisions intersecting but not crossing. A total of four surgeons had operated on the six patients in this series. We evaluated the visual acuities without correction and the best-corrected visual acuities obtainable with spectacle and contact lens correction. Keratotomy and photokeratoscopy were also performed. Attempts were made to fit these eyes with rigid gas-permeable lenses to achieve better visual acuity than was obtainable with spectacles (ten eyes) or because the patient could not tolerate the amount of cylinder required in the spectacle plane (one eye). The contact lenses used were of the Boston IV material with a standard diameter of 9.2 mm, optical zone of 7.8 mm, and a tri-curve/lens design.

Results

All eyes except two, by history, had 20/20 best-corrected visual acuity with spectacles preoperatively. In two eyes (Patient 3) visual acuity was limited by refractive amblyopia. According to the patient, her visual acuity had never been correctable to 20/20, and she stated she had been told that this resulted from the failure to correct her refractive error during childhood. On examination, there was no evidence of lenticular opacity, retinal lesion, or optic nerve dysfunction to otherwise explain the decreased visual acuity.

At initial examination, all eyes had a decrease in best-corrected visual acuity with spectacles, ranging from 20/25 to 20/70 (Table). Only five eyes had a visual acuity of 20/40 or better with spectacles. In all eyes, contact lenses provided better visual acuity than could be obtained with spectacles, and all but one eye achieved a visual acuity of 20/40 or better with contact lenses. The remaining eye (Patient 3) had a history of amblyopia. Nine of 11 eyes could be successfully fitted with rigid gas-permeable

Accepted for publication Oct. 6, 1988.
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TABLE
PATIENT VARIABLES AFTER RADIAL AND ASTIGMATIC KERATOTOMY

PATIENT	UNCORRECTED VISUAL ACUITY	BEST-CORRECTED VISUAL ACUITY		KERATOMETRY (D)	SPHERICAL EQUIVALENT (D)	TIME AFTER SURGERY (MOS)
		SPECTACLES	CONTACT LENS			
Patient 1						
R.E.	20/200	20/60−2	20/40	37.5/39.5	+0.75	5
L.E.	20/50−2	20/40	20/30	38.0/40.25	−1.12	5
Patient 2						
R.E.	2/200	20/50	20/25	35.75/37.0	−1.37	24
L.E.	20/100	20/60	20/30	36.25/41.5	−0.87	22
Patient 3						
R.E.	20/400	20/70	20/60	35.5/35.85	+2.37	30
L.E.	20/200	20/50	20/40	35.5/37.0	+1.75	30
Patient 4						
R.E.	20/60	20/50	20/25	41.25/44.0	−1.12	48
L.E.	20/50	20/25	20/20	41.75/44.75	−0.87	48
Patient 5						
R.E.	20/300	20/40	20/25	32.0/36.75	−0.50	12
L.E.*	20/60	20/20	20/20	36.25/37.0	−1.37	12
Patient 6						
R.E.	20/200	20/40	20/25	43.5/48.5	−4.12	60
L.E.	20/80	20/30	20/20	44.0/45.0	−3.75	60

*Incisions did not intersect in this eye (Fig. 4).

contact lenses. In two eyes, because of the marked topographic distortion, the lenses consistently decentered and could not be worn successfully.

Slit-lamp examination in each case demonstrated an intact epithelium over the incisions. Typically, in the areas where the incisions intersected, there appeared to be separation of the edges of the incisions. The gap was filled with a white material thought to represent epithelial plugs that extended down into the incisions (Fig. 1).

Photokeratoscopy demonstrated irregular astigmatism that varied from moderate (Fig. 2, left) to marked (Fig. 3, right). The irregular astigmatism was primarily localized to the meridians with intersecting incisions.

An instructive comparison was afforded by the photokeratoscopic findings in Patient 5. In the right eye (Fig. 3), combined radial and astigmatic incisions were created, with the transverse incisions crossing the radial incisions. This cornea shows marked irregular astigmatism. The eye could not be successfully fitted with a contact lens because of persistent lens decentration. With spectacles, visual acuity in this eye was 20/40. In the left eye, nonintersecting radial and astigmatic incisions were performed; this eye has only mild, nonproblematic irregular astigmatism (Fig. 4). With spectacles, visual acuity in this eye was 20/20.

Discussion

In 1985 Karr, Grutzmacher, and Reeh[1] described a 35-year-old man whose combined radial and transecting circumferential incisions were complicated by wound gape, persistent epithelial defect, and sterile ulceration with perforation. This patient required penetrating keratoplasty. Pathologic examination of the excised corneal button demonstrated persistent epithelial plugs in some incisions, but showed fairly well-developed healing in the radial incisions. Girard and associates[2] performed arcuate incisions for astigmatism six months after radial keratotomy in one patient. The corneal wounds from the radial keratotomies opened with the arc incisions, and healing of the gaping wounds was slow and required a therapeutic soft contact lens. Deg, Zavala, and Binder[4] described two patients who required penetrating keratoplasty after radial keratotomy; during trephination, radial incisions in the recipi-

Fig. 1 (McDonnell, Caroline, and Salz). Biomicroscopic photograph demonstrates area of intersecting radial and tangential incisions. Although surface epithelium is intact, edges of incision are separated and incisions are filled with large white epithelial plugs.

ent cornea separated easily, necessitating suturing of the peripheral incisions in one of the eyes. Robin and associates[5] reported a similar case. Thus, there is extensive evidence, in the form of case reports, that the intersection of tangential or circumferential incisions with radial incisions can lead to delayed wound healing. Despite this accumulating evidence, the placement of intersecting corneal incisions continues. Three of the eyes in this series underwent surgery within the last 1½ years (one eye, September 1987; two eyes, April 1988). In all of these eyes, purposefully intersecting (crossing) incisions were created, as illustrated in Figure 4. In one eye (Fig. 1), flagged incisions were also present, with an intentional but not crossing intersection.

Some irregular astigmatism can occur with radial incisions alone. In the Prospective Evaluation of Radial Keratotomy (PERK) Study,[6] the central two or three circles of the photokeratoscope were found to be regular because they overlaid the central clear zone and the peripheral six of seven circles showed a slight irregularity, because they overlaid the corneal scars. One patient in the PERK Study with monocular diplopia and irregularity over one incision had the wound opened, "cicatricial tissue" excised, and the wound sutured. This resulted in improvement, but not complete resolution, of the topographic irregularity and monocular diplopia. Our experience suggests that an important complication of intersecting radial and tangential or circumferential incisions is irregular astigmatism that cannot be corrected with spectacles. Nonhealing epithelial defects, sterile ulceration, and technical difficulties that may be encountered in performing penetrating keratoplasty are clearly worrisome potential complications, but are either less frequent or are less likely to be referred to our institution for management.

With radial or combined radial and noninter-

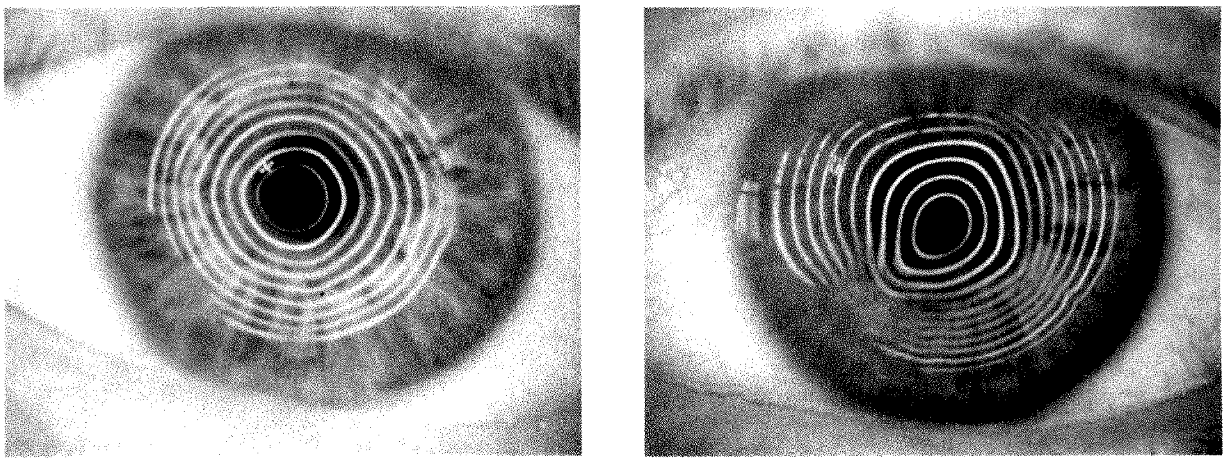

Fig. 2 (McDonnell, Caroline, and Salz). Left, Patient 3, left eye. Moderate irregular astigmatism after intersecting radial and transverse incisions. Right, Patient 2, left eye. Marked irregular astigmatism after intersecting radial and transverse incisions.

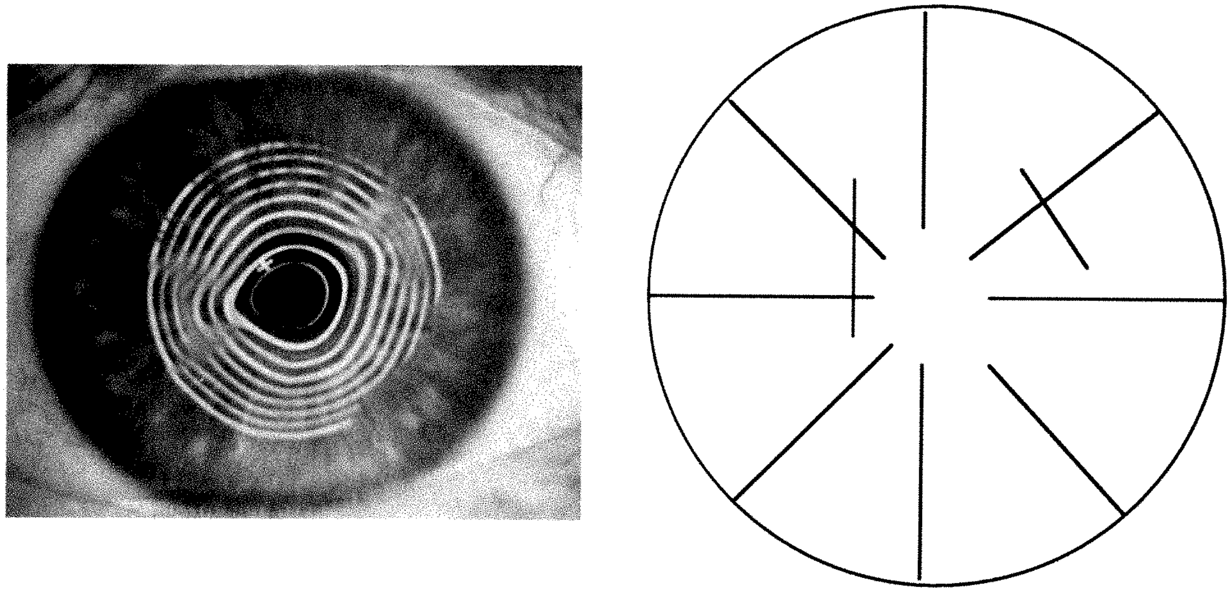

Fig. 3 (McDonnell, Caroline, and Salz). Patient 5, right eye. Left, Marked irregular astigmatism following intersecting radial and transverse incisions. Right, Schematic illustration of keratotomy incisions in this cornea.

secting transverse incisions, the corneal topography is dramatically altered but the corneal contour remains fairly regular in shape.[7,8] Postoperative rigid gas-permeable contact lens fitting in this population has proven successful.[9,10] In those patients with markedly irregular topographies because of intersecting incisions, we have not been uniformly successful in fitting contact lenses. In patients for whom contact lens fitting is not successful, the available options include having the visual acuity limited to that provided by spectacles, performing a

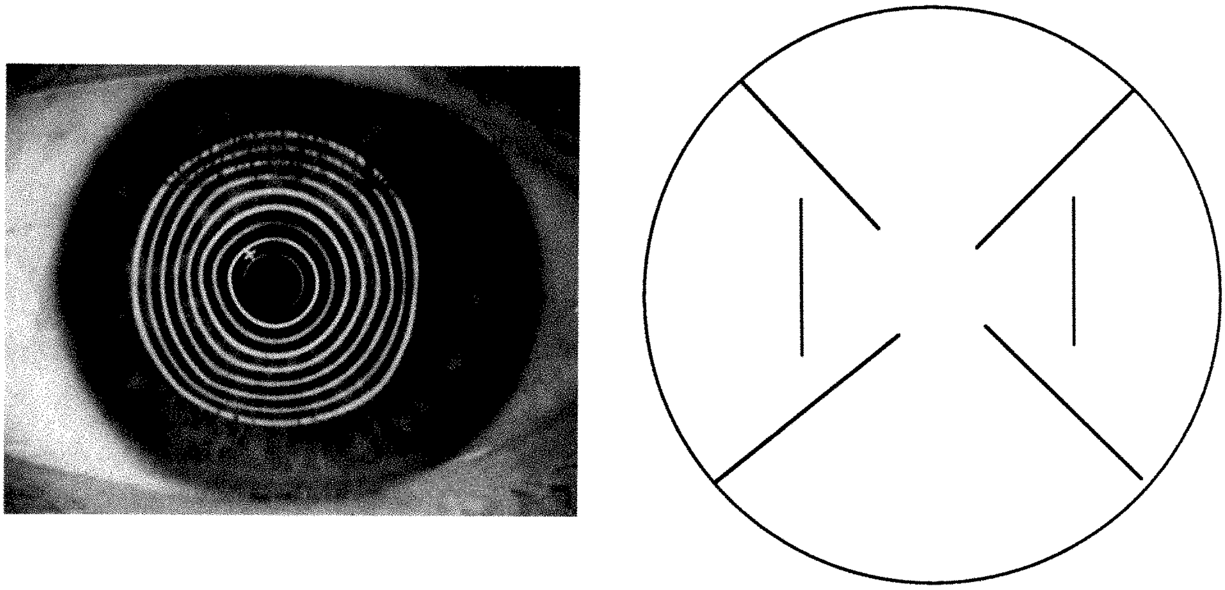

Fig. 4 (McDonnell, Caroline, and Salz). Patient 5, left eye. Left, Minimal irregular astigmatism after combined radial and transverse keratotomies without intersection of incisions. Right, Schematic illustration of keratotomy incisions in this cornea.

penetrating keratoplasty, or attempting to remove the epithelial plug from the site of incision crossing and resuturing the incisions. Penetrating keratoplasty may be technically difficult after radial keratotomy,[4,5] however, and the success rate with resuturing of incisions to reduce irregular astigmatism is unknown.

Selection of an appropriate base curve for a contact lens may be difficult after radial keratotomy because of the disproportionate amount of flattening in the central as compared to the midperipheral cornea. Keratometry measures only the central 3-mm average corneal curvature, and fitting a contact lens with a base curve equal to the keratometry reading results in an excessively flat lens/cornea relationship. A computerized corneal topographic analysis system has proven useful as an aid to contact lens fitting by allowing accurate measurement of the midperipheral corneal topography, with subsequent contact lens fitting to match this topography.[8] If the topography is excessively distorted, however, we found in two of our patients that the contact lenses will decenter despite efforts to solve this problem by varying the base curve or lens diameter.

Because of the nature of our practice, which consists solely of referred patients, it is not possible for us to comment on the frequency with which irregular astigmatism is a problem after the creation of intersecting radial and tangential or circumferential corneal incisions. Nonetheless, we infer from the number of these cases seen in consultation at our institution (three eyes within the last 1½ years) that the problem is not uncommon. The results in the patients described herein should stimulate those surgeons who currently create purposefully intersecting (crossing) incisions to reconsider the wisdom of using this technique.

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Excimer Laser-Processed Donor Corneal Lenticules for Lamellar Keratoplasty

Shimon Gabay, Ph.D., Allan Slomovic, M.D., and Tony Jares, Ing.C.

We used the 193-nm argon-fluoride excimer laser to cut plano corneal lenticules from fresh corneal tissue for lamellar keratoplasty. The laser was used to cut away all corneal tissue outside a specially designed mold, which was developed to obtain a corneal lenticule of 10 mm in diameter and a constant thickness of 0.3 mm. The surface topography of the excimer laser-cut corneal lenticule was smoother and more regular on scanning electron microscopy than a hand-cut corneal lenticule, and the thickness was constant around the surface. No thermal or mechanical damage to the cornea was observed on light microscopy in the area adjacent to the cut.

For lamellar keratoplasty, the lamellar dissection of the donor corneal lenticule is usually performed by hand at the time of surgery.[1] However, this technique is time-consuming and the surface topography of the cut is frequently uneven and irregular, leading to opacification at the graft-host interface. Additionally, the thickness of the lenticule is frequently irregular, and if the lenticule is accidentally perforated at the time of lamellar dissection the operation must be canceled.

Recently, cryolathic corneal lenticules measuring 10 mm in diameter with a constant thickness of 0.3 mm have been used for lamellar keratoplasty.[2] This tissue is then lyophilized for storage and can be shipped wherever necessary. The disadvantages of this procedure are that in the processes of freezing and lyophilizing the tissue, keratocytes are destroyed[3] and the interfibrillar collagen distance is modified.[4] This results in a delayed clearing of up to several months of the transplanted lenticules. The cost of preparing such a lenticule may also be prohibitive, up to $1,000.

In the last few years, the excimer laser has been found to be an excellent tool for cutting corneal tissue.[5-10] The 193-nm wavelength of the argon-fluoride excimer laser was found to have the lowest ablation energy threshold[9] and minimal thermal damage.[8,9] The ablation of corneal stroma at 193 nm also produced the most precise[7] and smooth surface cut.[8]

In a comparative study of frozen and nonfrozen human corneas, the fresh, nonfrozen tissue provided better clinical results than did frozen or freeze-dried tissue.[11] In an animal study, lenticules cut from nonfrozen corneal buttons using the excimer laser were transplanted in rabbit eyes and showed good clinical results, manifested as tissue clarity and lack of haze at the graft-host interface.[12]

Therefore, using the 193-nm argon-fluoride excimer laser to cut fresh tissue can provide the advantages associated with fresh tissue, as well as a precise, smooth cut. Herein we describe our technique for processing donor corneal lenticules for lamellar keratoplasty, as well as the results of examination of the tissue cut by scanning electron microscopy and light microscopy.

Material and Methods

The procedure for cutting and preparing the lamellar corneal lenticule from a fresh human eye is illustrated in Figure 1. The excimer laser was filled with a mixture of fluorine, argon, neon, and helium to produce a laser beam at 193 nm. The rectangular laser beam profile was focused to a spot of 1.3 × 0.25 mm by a spherical lens of 200-mm focal length. The laser

Accepted for publication Sept. 29, 1988.
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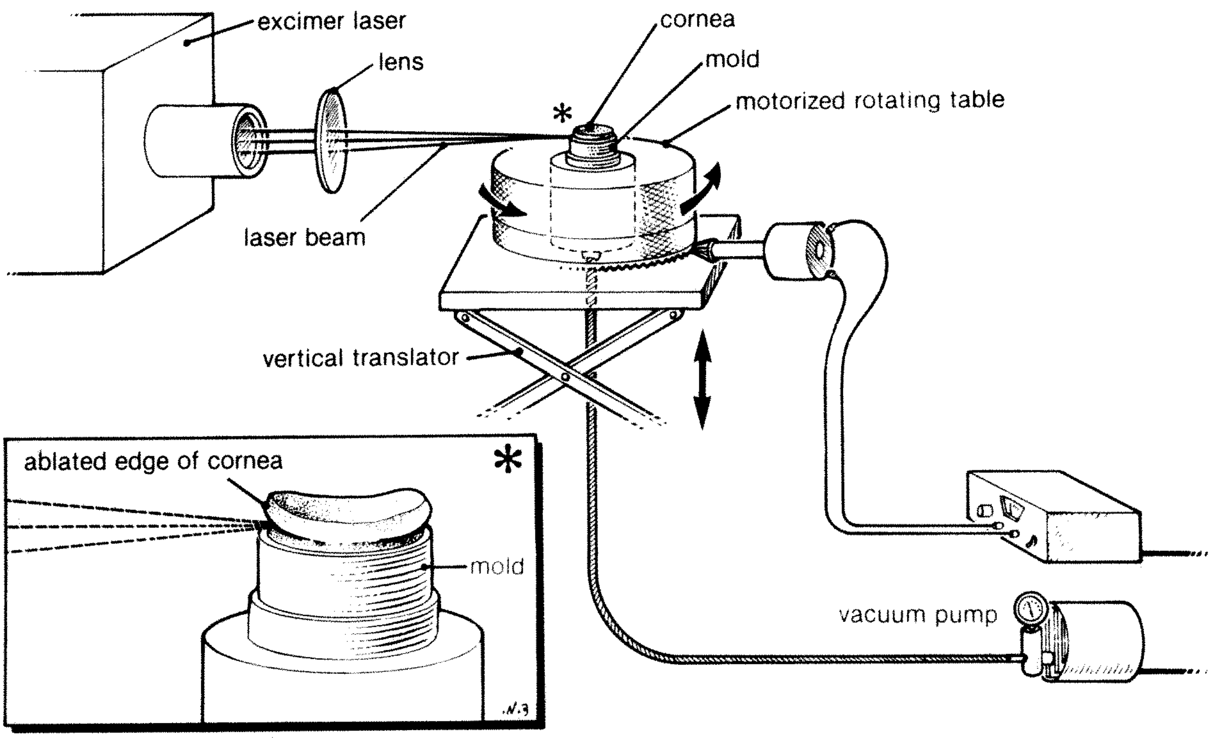

Fig. 1 (Gabay, Slomovic, and Jares). Schematic diagram of the lamellar corneal tissue processed by an excimer laser for lamellar keratoplasty. The lower left region presents an enlargement of the mold-tissue interface.

delivered pulses of 50-mJ energy in a 15-nS pulse width, at a repetition rate of 30 pulses per second. This resulted in irradiance of 15 J/cm^2 at the focus (or peak power of 3.3 mW/cm^2). The average laser beam power, measured by a power meter, was divided by the repetition rate to determine the pulse energy.

We developed a mold to obtain a corneal lenticule of 10 mm in diameter at a constant thickness of 0.3 mm. This mold was mounted on a motorized rotating turntable, which in turn was mounted on a vertical translator plate. This arrangement allowed us to adjust the vertical position of the mold in order to bring the mold's horizontal upper base flush with the focused laser beam.

Fresh corneal tissue, stored in chondroitin sulfate corneal storage medium, was obtained from the Eye Bank of Ontario, Canada. The tissue was placed on a curved silicone block, and a 10-mm universal trephine blade was used to cut a full-thickness, 10-mm diameter corneal button. This corneal button was mounted in the mold, with the epithelial side facing the mold surface, and was pulled against the flat base of the mold and held in place by a suction of 5 to 10 psi. During the laser cutting process, both the mold and the tissue were rotated at 1 rpm. The excimer laser beam was used to remove all corneal tissue above the mold within six to ten minutes. The prepared tissue was again stored in corneal storage medium and was sent to the operating room to be used for lamellar transplant. The mold, silicone block, trephine, and all the other components that were in contact with the corneal tissue during the cutting process were sterilized before the cutting process by glutaraldehyde solution for at least 20 minutes, then were rinsed with distilled water to remove any residuum, and finally rinsed with double distilled sterilized water.

Results

Using the arrangement illustrated in Figure 1, we cut and prepared corneal lamellae using two different techniques. In one technique we adjusted the upper base of the mold to be at the same horizontal plane as the laser beam, and

used the laser to cut in one corneal plane. In the other technique, the upper side of the corneal tissue was elevated to meet the laser beam level and the laser was used to ablate the upper corneal layer. Then, the mold was again elevated in order to ablate another corneal layer, and so on until the upper base of the mold matched the laser beam level. The first technique is faster, but the surface topography of the cut is not as smooth as that obtained using the second technique. This is because during the cutting process, each laser pulse produces a pressure wave that shocks and raises the tissue a small amount, allowing the following laser pulses to cut in different corneal layers. In the second technique, no significant pressure waves are generated, and the tissue is therefore stable during the cutting process. This results in ablation occurring in only one corneal layer.

Figure 2 presents comparative scanning electron micrographs of the surface topography of a corneal lenticule cut by hand in a fresh whole eye, with a guarded Castroviejo trephine and a No. 69 Beaver blade, and a lenticule cut by a 193-nm argon-fluoride excimer laser beam. The surface topography of the excimer laser-cut lenticule was smoother and more regular. In the tissue prepared by hand, the cut appeared to be in several stromal layers and the lenticule had residual corneal tissue of various sizes still attached to it.

The hand-cut lenticule also showed a mechanical disruption of the cut surfaces, which resulted in a changing of the order of the stromal collagen fibrils (Fig. 3). The excimer laser-cut lenticule, however, did not show any change in the stromal collagen order.

The main geometric features of the excimer laser-cut lenticule were best observed under light microscopy (Fig. 4). The salient features were the constant thickness of the lenticule (Fig. 4, top left), the lack of thermal and mechanical damage adjacent to the cut (Fig. 4, top right), and the normal corneal epithelium (Fig. 4, bottom left). Sometimes, a scratched silicone block may remove part of the epithelial layer when pressing the trephine against the silicone block during trephination. This leads to an uneven thickness of the laser-cut lenticule. In this case, the entire epithelial layer should be removed in order to obtain a lenticule of constant thickness. In general, all of the light micrographs in Figure 4 show regular corneal structure, no thermal damage, and survival of the keratocytes.

Discussion

The geometric features of the lamellae prepared by the technique described herein, as well as the clinical results in three patients who showed graft clarity from the first postopera-

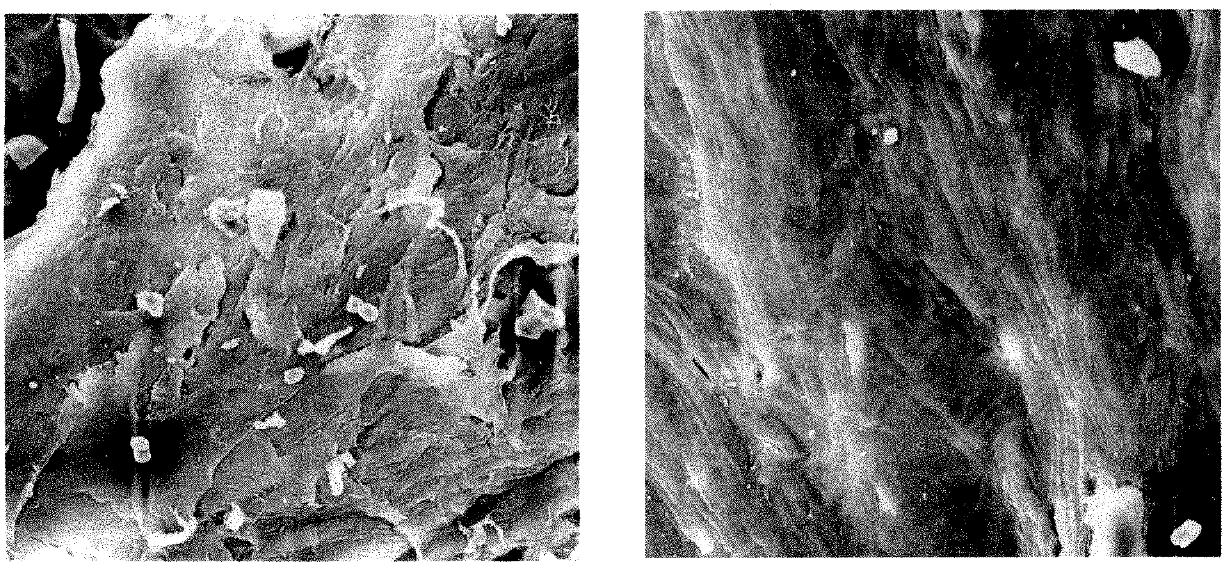

Fig. 2 (Gabay, Slomovic, and Jares). Scanning electron micrographs of a keratectomy prepared by hand using a lamellar dissector (left) and by 193-nm argon-fluoride excimer laser (right) (×350).

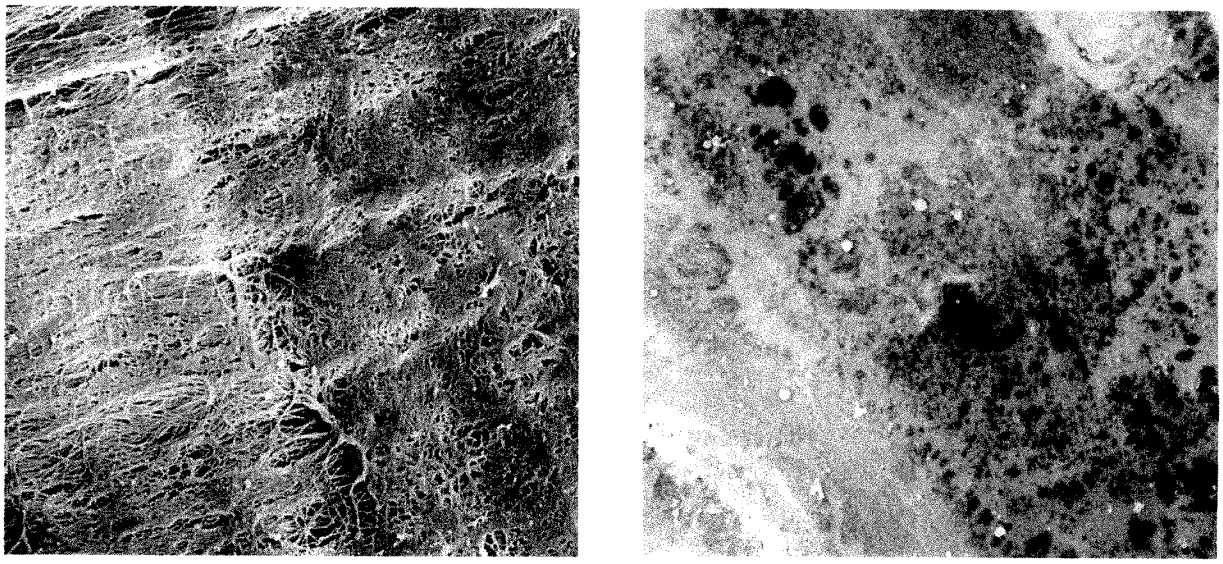

Fig. 3 (Gabay, Slomovic, and Jares). High magnification of scanning electron micrographs of a keratectomy prepared by hand (left) and by excimer laser (right) (× 6,000).

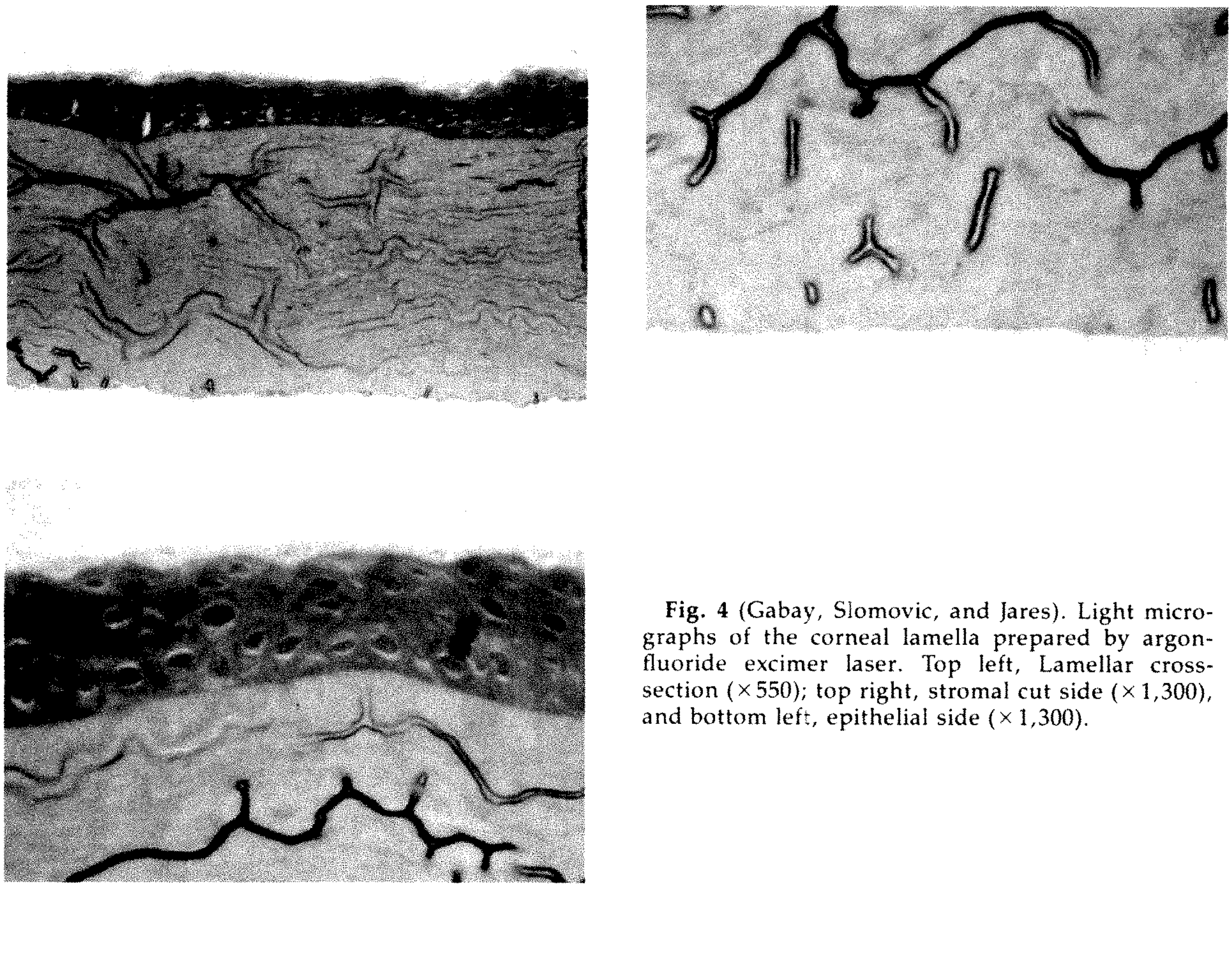

Fig. 4 (Gabay, Slomovic, and Jares). Light micrographs of the corneal lamella prepared by argon-fluoride excimer laser. Top left, Lamellar cross-section (× 550); top right, stromal cut side (× 1,300), and bottom left, epithelial side (× 1,300).

tive day (unpublished data), confirm that this technique is a straightforward procedure to process corneal lamellae for lamellar keratoplasty. The procedure is simple and does not require automatic control or on-line measuring of corneal thickness, which greatly increase the complexity and cost of the procedure. The cutting tolerance and quality depend only on the precise preparation of the mold and on the stabilization of the rotating table during the cutting process, both of which can be designed to meet high-performance standards. Although our laser cut did not produce as smooth a surface as expected, it was smooth enough to give good clinical results in graft clarity. Nevertheless, it should be improved by using a more stable vertical translator and rotating turntable.

The modification in the order of the stromal collagen fibrils, as found in the surface of hand-cut lenticules (Fig. 3, left), was the same as that found in stromal tissue after freezing and lyophilizing.[4] These modifications were not found in laser-cut lenticules (Fig. 3, right). This may explain why a clear graft, which depends on the distance between collagen fibrils,[13] results from the laser cutting process but not from the freezing and lyophilizing process. It also explains, in addition to the surface smoothness, the lack of haze in the graft-host interface[12] resulting from the laser cut but not from the hand cut. The same surface topographic findings were also reported by Kerr-Muir and associates[14] in a comparison study between conventional surgical and argon-fluoride excimer laser keratectomy.

In addition to using the excimer laser to process corneal lamellae, this technique can also be applied to process optical power lenticules for epikeratophakia. The only modification needed is to change the mold to provide a curved base, concave for hyperopia and convex for myopia, to produce the desired optical power.

Finally, the cost of preparing a lenticule by our technique does not exceed $100. Thus, it can be widely used for the many needs of corneal and refractive surgery.

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Edema of the Corneal Stroma Induced by Cold in Trigeminal Neuropathy

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A patient with a left sensorimotor trigeminal neuropathy was found to have edema of the corneal stroma induced by cold. Examination at room temperature demonstrated an anesthetic left cornea with minimal injection of the left eye and multiple punctate epithelial erosions. Corneal thickness, mean endothelial cell size, coefficient of variation of cell size, endothelial permeability to fluorescein, and aqueous humor flow rate, measured at room temperature were similar in the two eyes. After 47 minutes in a cold room at 4 C, the corneal thickness in the left eye increased from 0.55 to 0.65 mm, whereas that of the right eye remained at 0.55 mm. During the period of maximum swelling, the left cornea had clinical stromal edema with folds in Descemet's membrane but no epithelial edema. After return to room temperature there was a gradual return to normal corneal thickness over three hours. Fluorophotometry showed no evidence of increased endothelial permeability during corneal swelling in the left eye. Specular microscopy after 15 minutes of cold exposure demonstrated many swollen and irregular endothelial cells with darkened areas between cells in the left eye. Sensory nerve deficiency in the human cornea can produce an abnormal sensitivity to cold, resulting in defective control of corneal hydration. This study suggests that this effect may be on the endothelium.

In a recent study Thorgaard, Holland, and Krachmer[1] documented the development of corneal edema induced by cold in a patient with an ipsilateral trigeminal nerve palsy from a tentorial ridge meningioma. We examined a patient with sensorimotor trigeminal neuropathy who also had corneal edema induced by cold. This study provides further evidence that the trigeminal nerve may influence corneal hydration during exposure to low environmental temperatures.

Accepted for publication Aug. 24, 1988.

From the Department of Ophthalmology, Mayo Foundation, Rochester, Minnesota. This study was supported in part by National Institutes of Health grant EY 02037, Research to Prevent Blindness, Inc., and the Mayo Foundation.

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Case Report

A 50-year-old man first sought medical attention in February 1982 because of a one-year history of "a dead area over the left chin and left lower lip." Neurologic examination showed a decrease in sensation to pin prick in the distribution of the left mental nerve. By March 1985, the hypesthesia had progressed to include the left lower gingiva and side of the tongue. There was sparing of the first and second divisions and the motor component of the third division of the trigeminal nerve. Results of magnetic resonance imaging of the head performed in April 1985 were normal. Over the ensuing six months, involvement of the motor branch of the third division of the trigeminal nerve was noted. Results of a cerebral arteriogram were normal. The hypesthesia progressed to involve the maxillary division of the trigeminal nerve over the next 12 months. Computed tomography with contrast and magnetic resonance imaging of the brain performed in December 1986 showed a filling defect within the posterior aspect of the left cavernous sinus. Because of further progression of the hypesthesia during 1987 to involve the ophthalmic division of the trigeminal nerve, magnetic resonance imaging of the brain was performed in November 1987. The study showed an enlarged mandibular division and other trigeminal elements in Meckel's cavity.

The initial ocular complaint of blurred vision

in the left eye was noted in December 1987. These symptoms were first noted during snow skiing, but eventually occurred during any exposure to cold air. Episodes of decreased vision seemed to progress with time, occurring increasingly more rapidly after exposure to cold and requiring more time for resolution after returning to warm temperatures.

The patient was referred to our institution in April 1988. Best-corrected visual acuity was R.E.: 20/20 and L.E.: 20/25. Pupils, extraocular movements, and visual fields to finger counting were normal. The left temporalis and masseter muscles were atrophic. The conjunctival and episcleral vessels of the left eye were slightly injected. There was no lagophthalmos. Results of slit-lamp examination of the right eye were normal. The left cornea was noted to have multiple punctate epithelial erosions, which were more prominent inferiorly. There was neither epithelial nor stromal edema. The endothelium appeared normal by specular reflection. Results of the remainder of the anterior segment examination were normal. Corneal sensation was normal in the right eye and absent in the left eye. Central corneal thickness, measured with an ultrasonic pachymeter, was 0.55 mm in each eye. The fundi were normal. Radiographic studies were not repeated because surgery was planned elsewhere. A neurologic consultation documented the presence of an isolated left sensorimotor trigeminal neuropathy. A neurosurgical opinion agreed with surgical exploration for diagnosis. No further medical evaluation was performed.

Baseline measurements of endothelial permeability to fluorescein and aqueous humor flow rate at ambient temperature were performed in each eye the next day according to a previously published method[2] using a two-dimensional scanning ocular fluorophotometer[3] (Table). Wide-field specular microscopy of the central corneal endothelium was performed in each eye before cold exposure. Representative photographs are shown in Figure 1. Photographic negatives were projected at a magnification of ×500, and the areas of 100 individual cells were measured for each eye with an electronic digitizer. The mean endothelial cell size, mean coefficient of variation of cell size, and number of cell sides were determined for each eye from specular micrographs taken before cold exposure (Table). Polygonality was determined by counting the number of vertices or sides of each traced cell and was expressed as the percentage of cells with n sides for n = 5,

TABLE

BASELINE MEASUREMENTS AT ROOM TEMPERATURE

	R.E.	L.E.
Endothelial permeability to fluorescein, $\times 10^{-4}$ cm/min	4.33	4.20
Aqueous humor flow rate, μl/min	3.58	2.82
Mean endothelial cell size, μm^2	399	411
Coefficient of variation of endothelial cell size	0.23	0.22
Polygonality (%)		
Pentagonal cells	17	20
Hexagonal cells	69	68
Heptagonal cells	13	11
Octagonal cells	1	1

6, 7, and the like. The parameters were similar in the two eyes. Intraocular pressure, measured with a Goldmann tonometer, was 17 mm Hg in each eye.

On the following day the patient awoke at 4 A.M. and instilled one drop of 2% fluorescein into each eye. He then returned to sleep. After awakening several hours later, corneal thickness was measured in each eye using the ultrasonic pachymeter. In this, and all subsequent measurements of corneal thickness, the mean of three measurements was recorded. Because of unusually high patient motivation and cooperation, we were able to perform all measurements of corneal thickness in both eyes without anesthesia. Baseline measurements of corneal stroma and anterior chamber fluorescein concentrations were performed with the two-dimensional scanning ocular fluorophotometer. The patient was then placed in a 4-C cold room with a rotary fan set at moderate speed approximately 50 cm from the patient. Periodic measurements of corneal thickness were performed with an ultrasonic pachymeter. A gradual increase in the degree of injection of the left eye was noted with increasing time of cold exposure. Blinking, monitored without the patient's knowledge, was complete and symmetric in both eyes and averaged 30 to 35 blinks per minute during cold exposure. The patient was removed from the cold room after 47 minutes, at which time the corneal thickness was 0.56 mm in the right eye and 0.60 mm in the left eye. Visual acuity was 20/20 in the right eye and 20/25− in the left eye. Results of slit-lamp examination of the right cornea were normal. The left cornea had the previously noted punctate epithelial erosions. Moderate

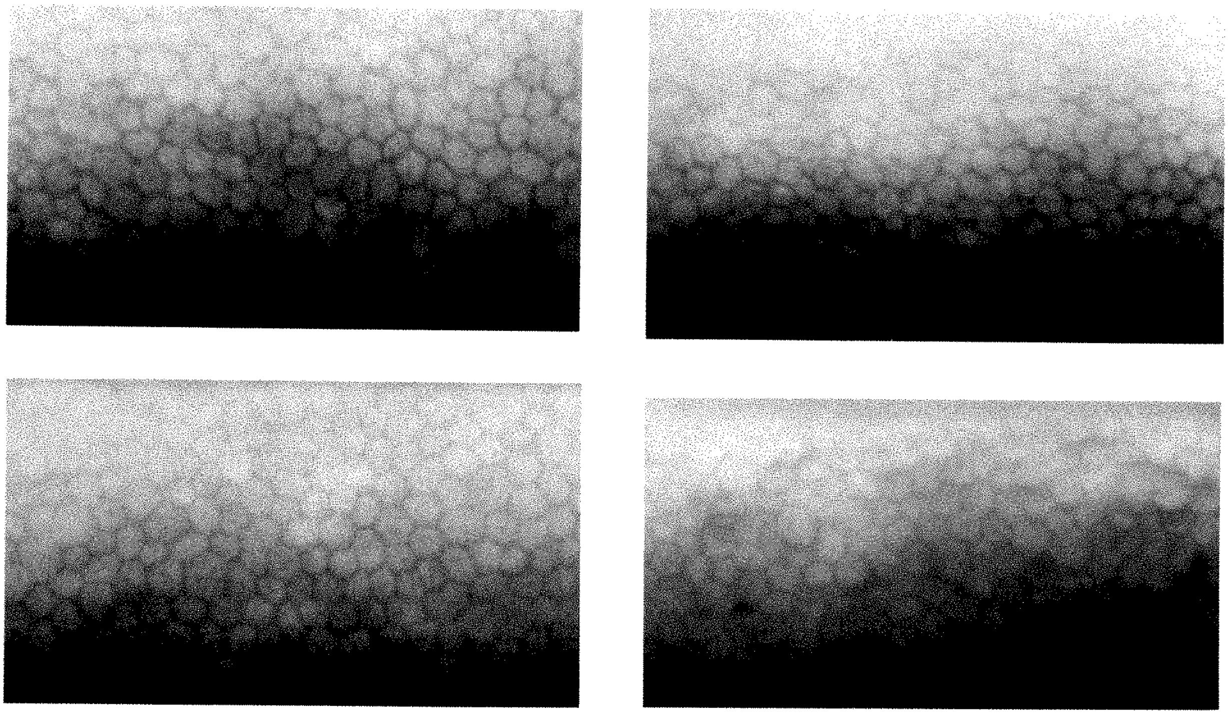

Fig. 1 (Wilson, Garrity, and Bourne). Corneal endothelial specular micrographs before cold exposure in the right control (top left) and left denervated (top right) corneas. After 15 minutes in a cold room (4 C), the structure of the endothelial cells of the right cornea (bottom left) appear unchanged; endothelial cells of the left cornea appear swollen and irregular, with darkened areas between cells (bottom right).

stromal edema with folds in Descemet's membrane were present. There was no epithelial edema.

Periodic measurements of corneal thickness, corneal stromal fluorescein concentration, and anterior chamber fluorescein concentration were performed for five hours after the patient left the cold. The corneal thickness in the right eye remained stable at 0.55 to 0.56 mm during and after exposure to cold (Fig. 2). In the left eye, there was an initial decrease in corneal thickness to 0.53 mm during the first ten minutes of cold exposure. This was followed by a period of rapid swelling that continued after removal from the cold to a corneal thickness of 0.65 mm. The swelling during this period was approximately linear and occurred at a rate of 2.3 μm/minute. The thickness remained at 0.65 mm for approximately one hour and then gradually returned to normal during the next three hours.

Measured fluorescein concentrations in the corneal stroma were corrected for corneal thickness with correction factors determined by measuring the fluorescence of a solution of known fluorescein concentration in a variable thickness chamber with a clear plano contact lens in front.[4] The back of the chamber was a black plano contact lens. The radius of curvature of the back surface of the black lens was 7.3 mm. Measurements were made at chamber depths from zero to 1.5 mm in 0.1-mm intervals. The correction factors were defined as the ratio of fluorescence in a thick chamber (1.5 mm or greater) to the fluorescence at the specified thickness.

In the right eye for approximately 30 minutes after removal from the cold, the stromal fluorescein concentration did not appear to change (Fig. 3). The subsequent decrease in stromal fluorescein concentration approached a first order process. In the left eye for approximately 30 minutes after cold exposure, there was a rapid decrease in stromal fluorescein concentration. When the change in fluorescein concentration between the initial measurement before cold exposure and the final measurement after corneal thickness had returned to normal in the left eye (Figs. 2 and 3) was calculated, however, the decrease in fluorescein concentra-

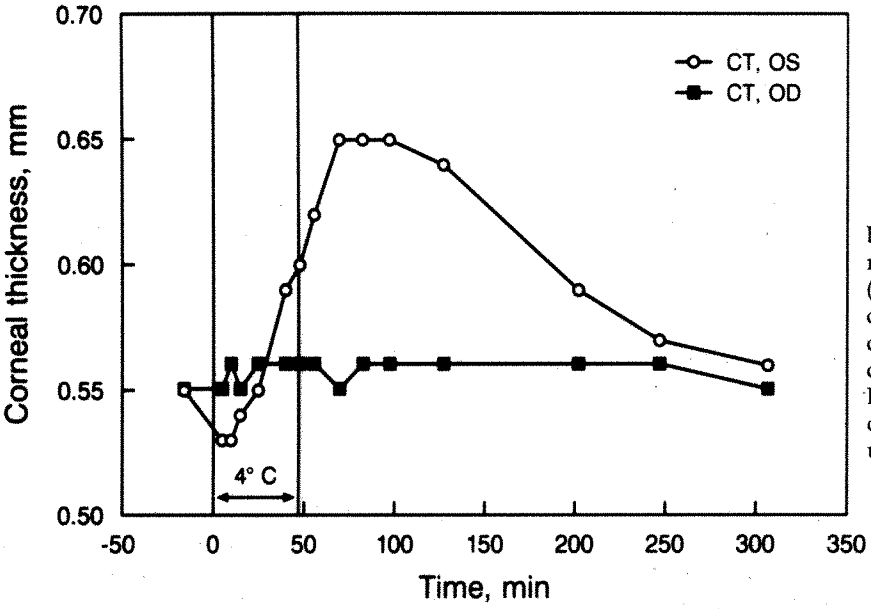

Fig. 2 (Wilson, Garrity, and Bourne). Central corneal thickness (CT) response to cold air (4 C) for 47 minutes in the right control and the left denervated corneas. The vertical bars indicate the period of cold exposure. Each point represents the mean of three measurements with an ultrasonic pachymeter.

tion in the right eye (75.6%) was greater than that found in the left eye (62.6%).

After six hours at room temperature the corneal thicknesses in the right and left eyes were 0.55 and 0.56 mm, respectively, and the patient was returned to the 4-C cold room with the rotary fan for 15 minutes. After leaving the cold, corneal thicknesses in the right and left eyes were 0.56 and 0.54 mm, respectively. Wide-field specular micrographs of the central corneal endothelium were taken immediately in each eye (Fig. 1). Endothelial cells in the right eye appeared unchanged compared with the photographs taken before cold exposure. In

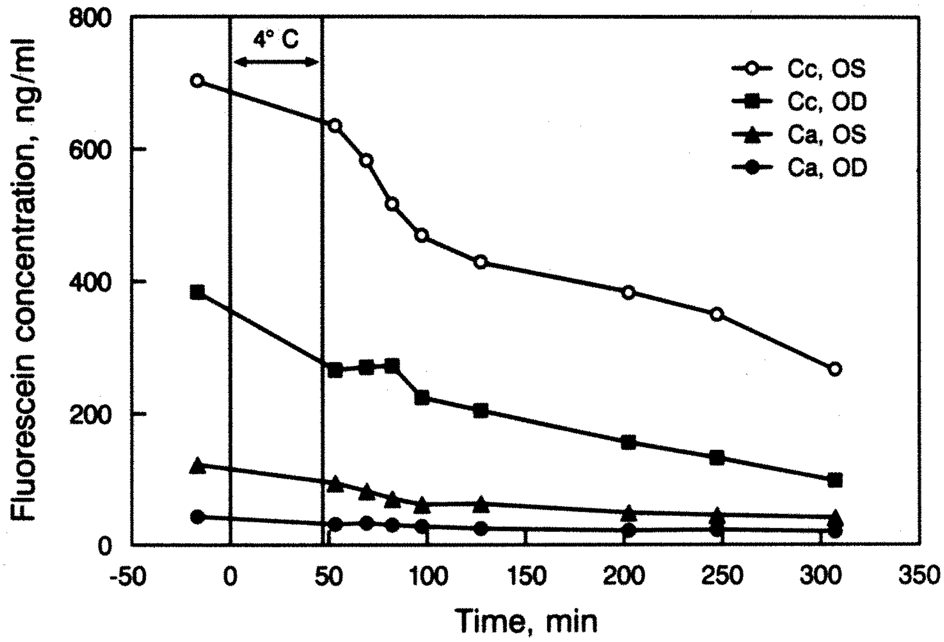

Fig. 3 (Wilson, Garrity, and Bourne). Change in central stromal (C_c) and anterior chamber (C_a) fluorescein concentration over time for the right control and the left denervated corneas. The vertical bars represent the period of exposure to 4 C for 47 minutes.

the left eye after cold exposure, however, many endothelial cells appeared swollen and irregular. Dark areas were also noted between groups of cells.

Basal lacrimal secretion was measured in each eye after instilling proparacaine anesthetic into both eyes. After five minutes, there were 8 and 10 mm of filter paper wetting in the right and left eyes, respectively.

Discussion

The findings in our patient provide further evidence that the trigeminal nerve may influence corneal hydration, as manifest during exposure to low environmental temperatures. The history and findings are similar to the patient described by Thorgaard, Holland, and Krachmer[1] who had an ipsilateral trigeminal nerve palsy caused by a tentorial ridge meningioma. In their study, the patient had stromal and epithelial edema with an increase in corneal thickness to 0.789 mm after two hours at 4 C in the eye on the side with trigeminal neuropathy. The authors were unable to determine the origin of the corneal edema since their study was confined to documenting the occurrence of stromal and epithelial edema after a prolonged period in the cold. In the present study, the lack of epithelial edema on slit-lamp examination during the period of maximal swelling after 47 minutes at 4 C and the presence of endothelial morphologic changes on specular microscopy after cold exposure suggest that this effect may be on the endothelium. The endothelial morphologic changes may have been secondary to stromal edema with folds in Descemet's membrane two hours before specular microscopy. When the specular micrographs were taken 15 minutes after cold exposure, however, there were no folds and the corneal thickness was 0.54 mm.

There was a relatively slow decrease in the stromal fluorescein concentration in the denervated left cornea during cold exposure (Fig. 3). This appears to have been followed by a rapid decrease in the concentration after returning to room temperature. The relative increase in stromal volume is not sufficient to account for the decrease in concentration, so that fluorescein appeared to leave the cornea more rapidly during this period. During the interval where stromal fluorescein concentration appeared to decline rapidly, however, the anterior chamber fluorescein concentration continued to decrease gradually. If a marked increase in endothelial permeability resulted in a rapid decline in stromal fluorescein concentration, then a parallel increase in anterior chamber fluorescein concentration should have been noted. When the change in stromal fluorescein concentration between the initial measurement before cold exposure and the final measurement after corneal thickness had returned to baseline in the left eye was calculated, the decrease in fluorescein concentration was actually greater in the right eye (75.6%) than in the left eye (62.6%). Therefore, the apparent stability of stromal fluorescein concentration during cold exposure followed by a rapid decline at warmer temperature may be an artifact resulting from difficulties in measuring fluorescence when the thickness and optical properties of the stroma are rapidly changing. If all of the available data are carefully analyzed, the present study suggests that the corneal swelling during cold exposure is not the result of a breakdown in endothelial barrier function.

There are several possible explanations for artifacts in the measurement of stromal fluorescein concentration during and after cold exposure. First, during swelling of the cornea, a solvent drag effect may be produced whereby fluorescein cannot diffuse against a new flow of water into the stroma. If this possibility were correct, an increase in fluid flow into the stroma might not be paralleled by an increase in fluorescein permeability and, therefore, an increase in endothelial permeability to water could go undetected. Second, increased water in the stroma may decrease stromal albumin concentration and result in an increase in the efficiency of fluorescence by a mass action effect on the interaction of albumin with fluorescein, resulting in reduced quenching of fluorescence. Third, an increase in light scattering may increase the average path length and the physical size of the optical window of the instrument. It is not possible with the data in the present study to ascertain which, if any, of these possibilities is correct.

The observation that the mammalian cornea swells in vitro when cooled to 4 C and that this effect is reversible upon rewarming was important in the development of the current understanding of endothelial function.[5,6] The effect is thought to be the result of a temperature-dependent decrease in endothelial pump function. Stromal swelling induced by cold has also been produced in the rabbit by passing ice-cold saline through a flow-through contact lens.[7] In that experiment, the stroma was noted to swell

at a rate of 0.5 μm/minute. In the present study, the maximum rate of corneal swelling was 2.3 μm/minute and could, therefore, be consistent with a decrease in endothelial pump function resulting in corneal edema.

There have been several studies on the effect of cold on corneal hydration in mammals. Bito, Roberts, and Saraf[8] observed that the cornea of the hibernating woodchuck is able to maintain hydration despite a temperature of 9 C. They attributed this to a maintenance of the balance between endothelial pump and barrier function at the lower temperature in vivo. Hodson[9] studied rabbit corneas in vitro and believed that as the temperature was decreased from 35 to 25 C, corneal hydration was maintained because the decrease in pump rate was paralleled by a compensatory decrease in endothelial permeability. Similarly, Green and Downs[10] studied isolated rabbit corneal epithelium and endothelium. They reported that the flow of water across the epithelium and endothelium is decreased as temperature is decreased. Baum, Maurice, and McCarey[11] also found that flow resistance of the rabbit endothelium at 2 C increased 2.12 times over its value at 34 C. They, however, believed that this could be attributed to a proportional increase in the viscosity of water at the lower temperature. In the present study, after exposure to cold there appeared to be a period of approximately 30 minutes during which the endothelial barrier function in the normal right eye was markedly reduced. This is suggested in Figure 3 by the relatively constant stromal fluorescein concentration for the three measurements immediately following cold exposure in the right eye as corneal thickness remained stable.

During the period of most swelling, the rate of stromal thickening expressed as a percent of the initial corneal thickness was 0.42%/minute. In a study performed in rabbits, Maurice and Giardini[12] found that if the epithelium was completely removed, the stroma swelled at a rate of 0.5%/minute. Thus, this rate of swelling could be consistent with a complete breakdown of epithelial barrier function. While the cornea was maximally swollen, however, the epithelium remained normal without the edema that may have been expected if large amounts of water were leaking across the epithelium. Therefore, interference with epithelial function as a mechanism for corneal swelling seems unlikely, but cannot be dismissed with certainty based on the present observations.

Histopathologic and embryologic studies have demonstrated that nerves enter the cornea radially from the corneoscleral limbus. Most of these nerves repeatedly subdivide to form a plexiform system within the anterior stroma and, subsequently, penetrate Bowman's layer to innervate the epithelium.[13-16] Two studies have reported innervation to the corneal endothelium in the rabbit.[16,17] One of these studies also reported an unsuccessful search for corneal endothelial innervation in humans.[16] There is, therefore, no evidence available at the present time for direct innervation to the corneal endothelium in humans that could explain the apparent effect of a trigeminal neuropathy on endothelial function.

The development of neuroparalytic keratitis is a frequent complication of a trigeminal neuropathy.[18] Many studies have demonstrated neurotrophic effects on the corneal epithelium. Alper,[19] in a study of the rhesus monkey, found that after interruption of the trigeminal nerve supply to the cornea, the thickness of the epithelium was decreased on the affected side. Another study[20] reported a decrease in the rate of epithelialization of a corneal abrasion and an increase in epithelial permeability to fluorescein in rabbits after destruction of the trigeminal corneal nerve supply. Sigelman and Friedenwald[21] found a decrease in the rate of mitosis of the corneal epithelium in rats after trigeminal denervation. Mishima[22] reported effects of both the sympathetic and trigeminal nerves on the mitotic rate in corneal epithelium in rabbits. Sympathetic denervation caused a slight increase in the mitotic rate, followed by a marked decrease after approximately 16 hours. Sympathetic stimulation also caused a marked decrease in the mitotic rate. Trigeminal denervation and stimulation resulted in a decrease and increase, respectively, in the mitotic rate of the corneal epithelium. Vannas and associates[23] studied the effects of local corneal denervation produced by corneal surgery. Patients with previous corneal incisions from cataract or transplant surgery were subjected to hypoxic stress tests. These subjects manifested less corneal edema in the operated on eye compared with the unoperated on control eye. The degree of swelling correlated inversely with the cornea-touch threshold and directly with epithelial oxygen uptake. They hypothesized that the corneal incision reduced the metabolic activity of the epithelium because of an interruption of the nerve supply. Therefore, during hypoxic stress, there was a reduced demand for oxygen in the corneal epithelium on the operated on side, resulting in lower lactate production and less corneal swelling.

Effects of the trigeminal nerve on the regulation of corneal hydration by the endothelium would not necessarily have to be direct. Many studies have suggested that corneal epithelial cells produce soluble factors that can influence corneal stromal cells,[24-27] vascular endothelial cells,[28,29] neural tissue,[30-33] and immune cells.[24] The corneal epithelium or stromal nerves could similarly influence corneal endothelial function through the production of mediators that diffuse through the stroma and interact with the target tissue. Denervation of the epithelium could influence the production of such mediators and, therefore, indirectly affect the endothelium. This possibility is worthy of further investigation if there is no direct innervation of the human corneal endothelium.

Ortiz and colleagues[34] reported that a stream of cold air (−19 C) directed at the eye for 40 minutes had no effect on aqueous humor flow rate in humans. Therefore, it appears unlikely that a trigeminal neuropathy interferes with any mechanism whereby a compensatory increase in aqueous humor flow rate could serve to maintain endothelial temperature in response to decreased environmental temperature.

Many patients suffer trigeminal neuropathies as a result of surgical procedures, neoplasms, and other processes.[35-38] It is interesting to speculate why more patients have not been identified with a similar disorder of corneal hydration. Factors that may account for this include a lack of the necessary environmental exposure, nonreporting of symptoms by similar patients, or dismissal of symptoms without investigation by physicians because there are no signs at room temperature when the patient is examined. Alternatively, our patient and the patient described by Thorgaard, Holland, and Krachmer[1] may have some underlying physiologic difference that causes a susceptibility to this disorder after the development of a trigeminal neuropathy. Whatever the correct explanation, the importance of these two patients is the suggestion that the trigeminal nerve can influence corneal hydration by a previously unrecognized mechanism. Further investigations in humans and the development of an animal model are indicated so that the mechanisms involved can be better understood.

ACKNOWLEDGMENT

Richard F. Brubaker, M.D., assisted in interpreting the fluorophotometry data.

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Rapid Streptococcal Antigen Detection in Experimental Keratitis

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We assessed the role of commercially available immunodiagnostic procedures in comparison to Gram stain and culture in experimental bacterial keratitis. Rabbit corneas were inoculated with *Streptococcus pneumoniae, S. pyogenes, S. faecalis,* or *Haemophilus influenzae.* Corneal scrapings were processed before and during antibacterial therapy using a coagglutination assay to detect pneumococcal capsular antigen (Phadebact Pneumococcus test) and an enzyme immunoassay to detect group A streptococcal cell-wall antigen (TestPack Strep A test). In untreated infected eyes, both immunoassays were highly specific and as sensitive as Gram stain for detection of the respective microorganisms. For *S. pneumoniae* keratitis, the sensitivity of coagglutination was 82% and Gram stain, 73%. For *S. pyogenes* keratitis, the sensitivity of enzyme immunoassay was 100% and Gram stain, 62%. Immunoassays and Gram stain were less sensitive than culture during antibacterial therapy. Successful clinical application of the coagglutination assay in a patient with pneumococcal keratitis permitted early use of specific cephalosporin treatment.

Rapid, accurate diagnosis is helpful in the optimal management of microbial keratitis. Because bacterial cultures generally require at least 24 hours, the microscopic examination of Gram-stained smears is the most commonly used rapid diagnostic method, with a sensitivity of 60% to 70% for detecting microorganisms in corneal scrapings.[1] Recently, immunologic methods with enhanced sensitivity and specificity have been developed for the detection of microbial antigens in clinical specimens.

We evaluated two immunoassays that are in current clinical use for nonocular infections, require only five to ten minutes to perform, and test related microorganisms of ocular importance by particle-enhanced or enzyme immunoassay techniques.

We used a coagglutination assay for *Streptococcus pneumoniae* and an enzyme immunoassay for group A streptococci to determine their efficacy in comparison to Gram staining of corneal scrapings. These assay systems were evaluated before and during antibacterial therapy in experimental models of bacterial keratitis using *S. pneumoniae* or *S. pyogenes*. To assess specificity, potentially cross-reacting organisms, *S. faecalis* and *Haemophilus influenzae,* were also used. Our preliminary experience with the coagglutination assay in a patient with pneumococcal keratitis suggests a direct application for this technology in clinical practice.

Material and Methods

The left central cornea of 39 New Zealand white rabbits received a 0.1-ml intrastromal injection containing approximately 10^8 colony-forming units/ml. The fellow eye served as an uninfected control. Organisms selected for inoculation included human corneal isolates of *S. pneumoniae* (11 eyes), group A beta-hemolytic *S. pyogenes* (eight eyes), *S. faecalis* (ten eyes), and *H. influenzae* type b (ten eyes). All inoculated corneas developed suppurative keratitis within 24 hours as documented by slit-lamp biomicroscopy. Twenty-four hours after inoculation, both eyes were scraped with a sterile Kimura spatula and processed for Gram-stained smears, coagglutination for pneumococci, enzyme immunoassay for group A streptococci, and culture. A positive Gram stain was defined as two or more bacteria of appropriate morphology per smear. The order

Accepted for publication Oct. 10, 1988.

From the Sid W. Richardson Ocular Microbiology Laboratory, Cullen Eye Institute, Baylor College of Medicine, Houston. This study was supported in part by the Research to Prevent Blindness, Inc.

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of testing was randomly allocated to avoid bias in sampling error, and all tests were interpreted in a masked fashion by a single observer. Quantitative cultures were performed on excised corneas 24 hours after inoculation.

An additional 20 animals were similarly infected with *S. pneumoniae* (five eyes), *S. pyogenes* (five eyes), *S. faecalis* (five eyes), or *H. influenzae* (five eyes). Twenty-four hours after inoculation, topical therapy was administered, with one drop of cefazolin, 50 mg/ml, every hour for 12 hours. Scrapings were then performed for Gram stain, coagglutination, enzyme immunoassay, and culture. These rabbits were then killed and the corneas were excised for determination of quantitative cultures.

Coagglutination immunoassay—A staphylococcal coagglutination kit for detecting pneumococcal capsular polysaccharide (Phadebact Pneumococcus test, Pharmacia Diagnostics, Piscataway, NJ) was used. Unheated corneal scrapings were mixed on a disposable, white card with one drop of the test reagent containing polyvalent antipneumococcal antibodies coupled by the F_c region to protein A of heat-killed, methylene blue-stained staphylococci that permitted the free F_{ab} region to be available for homologous antigen-binding. The mixture was gently rocked for two minutes; visible agglutination, usually with clearing of the surrounding fluid, indicated a positive reaction. Negative controls using staphylococci coated with antibody from nonimmunized rabbits were performed for all samples. Positive controls were performed with a saline suspension containing approximately 10^8 colony-forming units/ml of a human corneal isolate of *S. pneumoniae*.

Enzyme immunoassay—An enzyme immunoassay to detect group A-specific streptococcal polysaccharide antigen (TestPack Strep A, Abbott Laboratories, North Chicago, Ill.) was used. Corneal scrapings were mixed with sodium nitrite and acetic acid reagents for five minutes for carbohydrate extraction by the micronitrous acid technique. After pH neutralization with buffer, the liquid extract was transferred to the reaction disk, which contained rabbit anti-group A carbohydrate fixed in a vertical line and group A carbohydrate in a crossing horizontal line. A conjugate of rabbit anti-group A carbohydrate and alkaline phosphatase was added. Washing, chromogenic, and stabilizing reagents were added sequentially. A purple cross indicated a positive reaction for the presence of group A carbohydrate in the specimen extract, and a purple horizontal bar alone provided a built-in procedural control to indicate a properly extracted specimen without group A carbohydrate antigen. A positive control was tested in parallel by using a human corneal isolate of *S. pyogenes*. The entire testing sequence was completed within ten minutes.

Culture technique—Corneal scrapings were directly inoculated onto 5% sheep blood agar plates by C-streaks. All plates were incubated in 5% CO_2 at 35 C for 24 hours. Microorganisms were identified by Gram stain and standard microbiologic criteria.[2] Quantitative corneal cultures were performed by homogenizing excised corneas after being rinsed in sterile saline, blotted dry, and weighed. Aliquots of the tissue homogenate were plated in duplicate on brain-heart infusion agar plates that were incubated for 24 hours at 35 C. The number of colonies was counted and adjusted to colony-forming units per milligram of corneal tissue.

Results

Test results of the contralateral uninfected cornea were negative by all testing methods. Five of six of the *S. pneumoniae*-infected corneas were correctly identified by the coagglutination assay, and all of the *S. pyogenes*-infected corneas were correctly identified by the enzyme immunoassay (Table). None of the corneas infected with either *S. faecalis* or *H. influenzae* tested positive by either diagnostic kit. Culture results confirmed the presence of the original infecting organism in each case.

Case Report

A 62-year-old woman developed acute suppurative keratitis with an overlying epithelial defect. Gram-stained smears showed gram-positive diplococci with acute inflammatory cells, and the coagglutination assay for *S. pneumoniae* was markedly positive. Topical cefazolin therapy, 50 mg/ml, every 30 minutes was begun. Twenty-four hours after initiation of therapy, repeat corneal scrapings showed a few gram-positive diplococci by Gram stain and a weakly positive coagglutination reaction. Topical therapy was reduced to hourly, and rescrap-

TABLE

COMPARISON OF RAPID ANTIGEN DETECTION METHODS WITH GRAM-STAINED SMEARS AND CULTURE IN EXPERIMENTAL BACTERIAL KERATITIS*

		PNEUMOCOCCAL COAGGLUTINATION		GROUP A STREPTOCOCCAL ENZYME IMMUNOASSAY		GRAM STAIN		CULTURE	
ORGANISM	NO.	NO. POSITIVE	SENSITIVITY (%)	NO. POSITIVE	SENSITIVITY (%)	NO. POSITIVE	SENSITIVITY (%)	NO. POSITIVE	MEAN CFU/MG
Pretreatment									
S. pneumoniae	11	9	82	0	—	8	73	11	3.4×10^6
S. pyogenes	8	0	—	8	100	5	62	8	8.9×10^7
S. faecalis	10	0	—	0	—	8	80	10	5.2×10^6
H. influenzae	10	0	—	0	—	8	80	10	6.4×10^7
Partial treatment†									
S. pneumoniae	5	0	0	0	—	0	0	5	8.2
S. pyogenes	5	0	—	0	0	1	20	5	4.1×10^3
S. faecalis	5	0	—	0	—	3	60	5	1.6×10^6
H. influenzae	5	0	—	0	—	3	60	5	1.9×10^6

*Sensitivity = assay true-positives/(true-positives + false-negatives) × 100% = assay- + culture-positives/culture-positives × 100%.
†Hourly topical cefazolin 50 mg/ml for 12 hours.

ings at 48 hours after initiation of therapy showed both a negative Gram stain and a negative coagglutination assay. Initial microbial cultures and rescrapings after 24 hours confirmed *S. pneumoniae*; no organisms were isolated after 48 hours of therapy. The infiltrate gradually resolved, and visual acuity stabilized at 20/100.

Discussion

Rapid antigen detection assays that accurately identify responsible microorganisms are of potential value in the evaluation of ocular infections. We evaluated commercially available microbial detection methods to assess their potential role in the diagnosis of streptococcal keratitis. We used animal models of bacterial keratitis produced by *S. pneumoniae* and *S. pyogenes* and chose *S. faecalis* and *H. influenzae* to assess specificity by using organisms of related immunogenicity.

We selected a pneumococcal test kit (Phadebact Pneumococcus) that uses a solution of antibody-coated, killed staphylococci to detect the presence of pneumococcal capsular polysaccharide by a coagglutination reaction. This technique of coagglutination was recently developed into a diagnostic test for pneumococci using laboratory reagents,[3-10] and clinical reports have subsequently assessed the commercial Phadebact kit for various body fluids of culture-proven pneumococcal infections. The sensitivity of the commercial assay has been reported as 25% to 100% for cerebrospinal fluid in meningitis,[10-18] 74% to 89% for sputum in pneumonia,[19-21] and 86% for serum in bacteremia.[22]

We also studied the role of an enzyme immunoassay for group A streptococci (TestPack Strep A) to detect group-specific cell-wall carbohydrate. Clinical studies with this assay have found a sensitivity of 73% to 96% for throat swabs of patients with streptococcal pharyngitis.[23-26]

Our study showed that these rapid diagnostic tests were useful for the identification of experimental *S. pneumoniae* or *S. pyogenes* keratitis. In comparison to Gram stain of untreated streptococcal keratitis, these assays were highly sensitive and, by detecting species-specific polysaccharides, lacked false-positive reactions to similar microorganisms.

Both Gram stain and the antigen detection methods were less helpful during partial therapy with a topical first-generation cephalosporin. The immunoassays' false-negative reactions could be the result of absorption of immunoglobulins and other host proteins to the surface of streptococci, thereby masking their antigenic sites. Low numbers of organisms in the specimen with available antigen below the minimally detectable concentration for the testing method would also result in a negative reaction. The quantitative culture data

showed that at least 10^5 colony-forming units/mg of cornea are required for a consistently positive Gram-stained smear. The threshold corneal concentration of viable streptococci necessary for a reactive antigenic assay on corneal scrapings is unknown but appears to be much less.

This study suggests a potential clinical role for these immunoassays in the rapid detection of streptococcal keratitis. Our experience with the coagglutination kit for *S. pneumoniae* in a patient with pneumococcal keratitis encourages further clinical use. While smears and cultures remain necessary, we predict an increasingly important and complementary role for diagnostic immunoassays in the initial evaluation of microbial keratitis. These assays are fast, simple to perform, easy to interpret, and do not require expensive equipment. While these immunoassays would miss a second organism in a polymicrobial infection and, therefore, do not replace culture, they could be good adjunctive tests for guiding early therapy. This study provides a basis for further investigations of immunoassay technology in the microbial antigenodiagnosis of corneal infections.

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OPHTHALMIC MINIATURE

She was fishing for trout in the canyon, Miss Cummins was reading a book, the horses were tied under the trees, Romero was fixing a proper fly on her line. He fixed the fly and handed her the line, looking up at her. And at that moment she caught the spark in his eye. And instantly she knew that he was a gentleman, that his "demon," as her father would have said, was a fine demon. And instantly her manner towards him changed.

D. H. Lawrence, "The Princess," *The Complete Short Stories, vol. II*
New York, Penguin Books, 1983, p. 483

DNA Cell Cycle Studies in Uveal Melanoma

Devron H. Char, M.D., Kim Huhta, B.S., and Frederic Waldman, M.D.

We histologically studied uveal melanomas treated with surgery only (enucleation or ciliochoroidectomy), low-dose (20 Gy) preenucleation radiation followed by enucleation, or enucleated melanomas after high-dose (50 to 80 Gy) charged-particle beam therapy. There was significantly less bromodeoxyuridine uptake in irradiated vs nonradiated melanomas ($P < .0001$). Similarly, tissue culture growth of irradiated tumors was significantly less ($P < .007$). These data demonstrate destruction of reproductive integrity of helium ion-irradiated melanomas. The incorporation of bromodeoxyuridine and fine needle aspiration biopsy techniques may be useful in the delineation of successfully irradiated tumors from tumors with apparent growth secondary to radiation vasculopathy.

THE GOAL of most radiation therapies is to destroy the reproductive integrity of a malignancy, but it may be difficult to determine whether this objective has been achieved.[1] Often, successfully radiated tumors are not completely obliterated, but a mass of sterile cells that cannot continue to propagate or metastasize remains. This problem is germane to uveal melanomas, since clinical, fluorescein angiographic, and ultrasonographic data may not accurately predict or document radiation efficacy.[1-4] Over 90% of uveal melanoma-containing eyes treated with either radioactive plaques or charged-particle beams are retained; however, the mean tumor shrinkage is only 40%, and less than 15% of tumors are reduced to a flat scar.[3-7]

Accepted for publication Oct. 10, 1988.

From the Ocular Oncology Unit, Department of Ophthalmology, the Francis I. Proctor Foundation (Dr. Char and Ms. Huhta) and the Laboratory of Cell Analysis (Dr. Waldman), University of California, San Francisco. This study was supported in part by an unrestricted grant from That Man May See, by National Institutes of Health grant EY0 7504, American Cancer Society grant PDT 321, and by grants from the Beal Foundation and the Richard and Gail Siegal Foundation.

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Irradiated uveal melanomas usually contain viable-appearing cells on histologic examination, although there is little or no evidence of mitotic activity.[8-14] In studies of other human malignancies, histologic evidence of mitotic activity has not correlated with tumor cell proliferation, and the detection of visible mitoses is an insensitive measure of cell cycling.[15-17]

Methodologic advances in flow cytometry and monoclonal antibody tumor cell labeling may be useful to elucidate the effect of radiation on the reproductive status of tumor cells.[18] The introduction of a thymidine analogue, bromodeoxyuridine, incorporated only during the synthesis phase of the cell cycle, and the use of an anti-bromodeoxyuridine monoclonal antibody, have simplified the problem of differentiating cycling from noncycling cells.[17,19-21] In both experimental studies and mathematical models, the bromodeoxyuridine uptake is stoichiochemically related to the number of cells in the synthesis phase.[17,22-24] Measurement of DNA synthesis by bromodeoxyuridine incorporation correlates closely with either autoradiography or ^{3}H-thymidine assays, but unlike the latter two assays, bromodeoxyuridine studies can be done rapidly, are more accurate, and do not require radiation exposure.[25-27]

If radiation therapy is completely effective, the number of cells synthesizing DNA should be reduced to near zero, and cells should stop cycling.[1] We used in vivo bromodeoxyuridine techniques to study the effects of two types of radiation on the cell cycle of uveal melanoma cells. Compared with melanomas removed without radiation, we observed a significant reduction in DNA synthesis after either 20 Gy of preenucleation radiation or after more than 60 gray equivalents (GyE) of helium ion charged-particle therapy.

Patients and Methods

All patients were treated at our institution between 1983 and 1986, and eventually had histologic documentation of a choroidal or ciliary body melanoma, or both. After the project

was approved by the human experimentation committee and both written and verbal informed consent was obtained, individuals were enrolled in the study.

All patients had intravenous injection of 200 mg/m^2 of body surface of bromodeoxyuridine one hour before surgery. Bromodeoxyuridine is incorporated by proliferating cells that are in the DNA synthesis phase of the cell cycle at the time of injection. Complete follow-up data were available and adequate tumor material could be analyzed in each case. Twenty-nine patients were included in the study (Table 1). One patient had bilateral primary uveal melanomas and the results of both eyes are reported. Eleven eyes were studied after primary enucleation and there were five ciliochoroidectomy tumor specimens. Five eyes were treated with 20 Gy of photon irradiation for five days before enucleation (five daily fractions of 400 cGy, usually followed by enucleation within 48 hours). Eight eyes were studied after

TABLE 1
PATIENT SUMMARY

PATIENT NO.	AGE (YRS)	TUMOR DIAMETER (MM)	ULTRASOUND HEIGHT (MM)		RADIATION	INTERVAL BETWEEN RADIATION AND ENUCLEATION	DOSE (GY)
			INITIAL	FINAL			
1	63	13.00	12.26	—	None	—	—
2	58	14.00	7.09	—	None	—	—
3*	66	15.00	10.72	—	None	—	—
4	79	12.00	10.34	—	None	—	—
5*	78	14.60	7.09	—	None	—	—
6*	79	R.E: 12.00	4.40	—	None	—	—
		L.E.: 10.50	7.09	—	None	—	—
7	22	18.00	13.41	—	None	—	—
8	73	12.00	3.45	—	None	—	—
9	71	18.00	9.96	—	None	—	—
10	42	17.00	13.50	—	None	—	—
11	61	12.00	7.66	—	None	—	—
12	66	15.00	11.87	—	None	—	—
13	45	20.00	12.26	—	None	—	—
14	67	19.50	4.79	—	None	—	—
15	62	24.40	3.00	—	None	—	—
16	35	15.00	9.97	—	None	—	—
17	67	22.50	7.47	—	Preenucleation radiation	24 hrs	20
18	67	15.00	9.19	—	Preenucleation radiation	24 hrs	20
19	69	20.00	12.45	—	Preenucleation radiation	24 hrs	20
20	56	18.00	14.50	—	Preenucleation radiation	24 hrs	20
21	75	18.00	9.96	—	Preenucleation radiation	24 hrs	20
22	64	18.00	8.62	8.62	He ion	13 mos	70
23	76	24.00	8.23	8.23	He ion	16 mos	70
24	52	13.00	6.32	4.79	He ion	25 mos	70
25	53	13.00	9.50	3.26	He ion	17 mos	70
26	71	7.00	5.17	3.64	He ion	48 mos	80
27	69	10.50	8.23	5.17	He ion	32 mos	60
28	71	13.00	6.13	3.83	He ion	24 mos	70
29	48	16.00	10.15	7.09	He ion	12 mos	70

*Cyclochoroidectomy.

enucleation, following helium ion therapy. The reason for enucleation after helium ion therapy was always complications caused by radiation, not evidence of tumor growth. Seven eyes were enucleated for intractable pain (four had neovascular glaucoma) and one for a blind, glaucomatous eye. The mean interval between charged-particle irradiation and enucleation was 25 months (range, 13 to 48 months) (Table 1).

Tissue processing—Most of the melanoma tissue was fixed in 10% formalin and processed in the conventional manner for standard light microscopic analysis. Paraffin-embedded sections, 8 μm thick, were cut, placed on glass slides, and stained for bromodeoxyuridine uptake as follows. The paraffin was removed from the sections with two ten-minute washes in xylene. They were then rehydrated through ten-minute washes in 100% ethyl alcohol, 95% ethyl alcohol, 70% ethyl alcohol, and finally distilled water.[28] The DNA was denatured by incubating slides for 20 minutes in 2-M HC1 and 0.5% Triton at room temperature, and then washing the slides twice in phosphate-buffered saline. The slides were then treated with 0.5% pepsin in 0.9-M saline, pH 1.5, for 30 minutes at room temperature. The slides were washed twice, then incubated with two different mouse anti-bromodeoxyuridine antibodies (Lawrence-Livermore Laboratories, Livermore, California) in a mixture of 1% bovine serum albumin and 0.5% Tween phosphate-buffered saline, for 30 minutes at room temperature.[29-31] The slides were washed twice with this solution and incubated in the dark with fluorescein-tagged goat anti-mouse IgG for 30 minutes. Slides were then washed twice, cover slipped, and observed on a fluorescence microscope at a magnification of ×40 under oil. A positive control retinoblastoma cell line, labeled in vitro with bromodeoxyuridine, was used to determine uniformity of bromodeoxyuridine staining with anti-bromodeoxyuridine monoclonal antibody. Under proper conditions, approximately 30% of the retinoblastoma tissue culture cells on each slide stained with bromodeoxyuridine.

All slides and tissue culture studies were analyzed in a masked manner. In all tumors we chose areas of viable-appearing cells to study bromodeoxyuridine uptake. Cells with disrupted cellular membranes, absent nuclei, and other evidence of necrosis were not counted. We looked for areas with higher bromodeoxyuridine uptake to increase the number of positive cells. Since tumors have areas with variable-labeling indices, we attempted to decrease false-negative data with this approach. The Figure shows a slide with cells that stained positively with anti-bromodeoxyuridine antibody. Bromodeoxyuridine labeling was expressed as the total number of positively stained, viable-appearing tumor cells in 32 fields at ×40 magnification.

Small pieces of fresh tissue were obtained from those enucleated eyes that had large enough tumors so studies did not compromise clinically important histopathologic analysis (15 patients). Ciliochoroidectomy specimens were not studied in this manner. A 1-mm^3 portion of fresh melanoma tumor tissue was mechanically dispersed in a sterile manner by mincing and then vigorously pipetting in phosphate-buffered saline. Cell viability was checked with trypan blue. Cells were split into two aliquots for fresh tissue cycle assessment or tissue culture studies. For bromodeoxyuridine studies, cells were pelleted and then resuspended in 70% ethyl alcohol, and fixed for 12 hours. Cells were then rehydrated with washes of 50% ethyl alcohol and distilled water. DNA denaturation and bromodeoxyuridine staining were performed as outlined above. Cells were washed twice, spotted on slides, and observed with a fluorescence microscope.

Fresh melanoma tissue was minced, and tissue culture explants propagated in 25-cm^2 flasks in 15 ml of RPMI 1640 medium supplemented with 15% fetal calf serum, glutamine, penicillin, and streptomycin. Flasks were fed once a week by removing 5 ml of spent medium and replacing it with fresh medium, and incubated at 37 C with 5% carbon dioxide. When

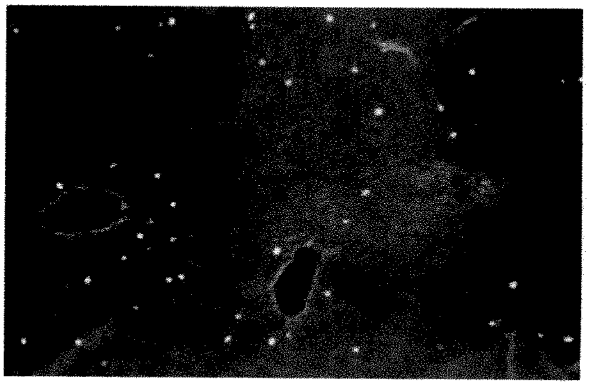

Figure (Char, Huhta, and Waldman). Fluorescence microscopy showing melanoma staining positive for bromodeoxyuridine (×10).

TABLE 2
TISSUE CULTURE OF UVEAL MELANOMAS*

PATIENT NO.	NO. OF PASSAGES	TIME IN CULTURE (WKS)	TREATMENT§	PERCENT TUMOR VIABILITY¶
1	12	20	Enucleation only	87
2	2	5	Enucleation only	39
3	5	13	Enucleation only	40
5	15	14	Enucleation only	60
7	15	14	Enucleation only	32
8	3	8	Enucleation only	46
12	5	14	Enucleation only	39
17	1†	4	Preoperative radiation	47
18	1†	4	Preoperative radiation	3
19	1†	4	Preoperative radiation	84
20	7	14	Preoperative radiation	36
21	3	6	Preoperative radiation	11
22	—‡	—	He ion	0
23	—‡	—	He ion	0
24	—‡	—	He ion	50

*Growth rates of the melanoma cells in culture were not constant but generally tended to decline steadily during the culture period, and often the cultures were overtaken by fibroblasts. Only two explants, from Patients 1 and 7, yielded stable cultures with reasonable growth rates, and the remainder were discontinued and stored in liquid nitrogen.

†Cells did not reach confluence on passaging.

‡Cells never grew to confluency.

§Preoperative radiation, 20 Gy; helium ion radiation, >60 Gy.

¶Original tumor viability determined immediately after surgery by trypan blue exclusion.

cultures reached confluency, they were passaged by trypsin treatment, diluted to one-third confluency, and seeded into three 25-cm^2 flasks. Cultures were watched until growth stopped or fibroblasts overtook the culture (Table 2).

In ten cases (five primary enucleations, two after 20-Gy preenucleation radiation, and three after helium ion therapy), we obtained fine needle biopsy specimens with a 25-gauge needle. The cells were placed in phosphate-buffered saline and their viability was assessed with trypan blue. Cells were then centrifuged and the pellet vortexed and fixed in 70% ethyl alcohol. These were processed for bromodeoxyuridine studies in the same way as other fresh tissue.

Cells analyzed by flow cytometry had two additional preparatory steps. Immediately preceding DNA denaturation, cells were incubated in 1-ml RNA'ase A (Sigma Chemical, St. Louis, Missouri), 1 mg/ml in phosphate-buffered saline at 37 C for 30 minutes, and washed once in 10 ml of phosphate-buffered saline. After the final wash, cells were counterstained in 1 ml of propidium iodide for at least 30 minutes before dual parameter analysis on the flow cytometer.

Samples studied by flow cytometry were run on a flow cytometer in list mode. The data were analyzed on a minicomputer. Photomultiplier tubes detected fluorescein (anti-bromodeoxyuridine), and propidium iodide fluorescence and forward scatter. The laser was set at 488 nm to excite fluorescein; emissions were detected through a 530 ± 30-nm filter. Propidium iodide was excited at 488 nm and emissions were detected through a 580-nm long pass filter. Ten to 20 thousand cells were counted. Statistical analysis was performed using Fisher's exact test, Kendall's Tau B test, and Pearson's correlation coefficient.

Results

There were more melanoma cells in the DNA synthesis phase in tumors that were not treated with ionizing radiation as compared to those in irradiated uveal melanomas ($P < .0001$). The mean bromodeoxyuridine count in 32 high-power fields in melanomas removed without radiation was 79.5 (approximately 1% to 10% of cells in the synthesis phase). In contrast, the

mean number of cells staining with bromodeoxyuridine after 20 Gy of preenucleation radiation was 0.8. In six eyes enucleated after helium ion irradiation without evidence of tumor growth after treatment, the mean count was zero.

In some tumors, we compared the bromodeoxyuridine values obtained with fluorescence microscopy to data obtained using two-parameter flow cytometry. Generally, the results were similar. Tumors with relatively few or no cells in DNA synthesis had low counts with both methods, whereas tumors with greater numbers of cells in synthesis phase had higher bromodeoxyuridine uptake with both techniques. We chose to rely on our microscopic data since they allowed us to eliminate artifacts caused by either staining of debris or nontumor cells infiltrating the melanoma.[31]

Nonparametric analysis was used to study possible correlations between cell type, tumor diameter, quantitative ultrasonographic thickness, histologic evidence of mitosis per high-power field, length of time between radiation and enucleation, and bromodeoxyuridine uptake. We observed no correlation between any of these factors and bromodeoxyuridine uptake.

We compared the fine needle biopsy specimen bromodeoxyuridine results with standard histologic sections and flow cytometry of the same tumor. These results were similar, although the sample size was too small to draw significant conclusions.

We were unable to propagate any long-term, rapidly growing tissue culture cell lines from the uveal melanoma specimens. In seven nonirradiated tumors, the uveal melanoma explants remained viable for three to 15 passages. Two of five samples from tumors that received 20 Gy of preenucleation radiation were maintained for three and seven passages; the other three tumors failed to grow in vitro. Of the three helium ion-irradiated samples, none could be established as a replicating uveal melanoma explant (Table 2). The difference between radiated and nonirradiated tissue culture results was significant (Fisher's exact test, $P < .007$).

Discussion

It is often difficult, clinically or with standard histologic techniques, to determine whether radiation has destroyed the reproductive capacity of tumor cells.[32] A number of investigators have demonstrated that viable tumor cells can remain in situ after successful radiation destruction of their reproductive capacity, and histologic evidence of mitosis is an insensitive gauge of tumor cell proliferative capacity.[15,16] Uveal melanoma cell cycling, as measured by the number of cells in the DNA synthesis phase, appears to have stopped after 20 Gy of preenucleation photon radiation or greater than 60 GyE of helium ion therapy. Tissue culture findings that irradiated melanoma cells were less capable of forming expanding explants as compared with nonirradiated melanomas support these results, as does the absence of mitoses noted in histologic sections of enucleated helium ion-treated eyes.[8]

The relationship of cell division to radiation response has been studied since 1906.[33] High-dose radiation results in immediate cell death or sterilization, most commonly as a result of double stranded DNA breaks associated with chromatid exchange, acentric or dicentric chromosomes, or micronuclear fragments.[1,34] In the interval between radiation and eventual cell destruction, giant cell formation, mitotic delay, and chromosome aberrations can occur.[35] At moderate doses of radiation (less than 20 Gy), tumor cells often remain viable and may complete one or two divisions before death.[1] Generally, over 99% of tumor cells lose their reproductive integrity after treatment with more than 20 Gy of radiation. Melanomas enucleated a mean of two years after helium ion irradiation were almost certainly composed of cells that were reproductively sterile. We cannot be certain that melanomas removed 24 to 48 hours after 20 Gy of preenucleation photon irradiation were in temporary or permanent cycle block.

In uveal melanomas with equivocal growth after irradiation, a fine needle biopsy combined with bromodeoxyuridine studies may ascertain whether the tumor is still cycling or whether growth could reflect intratumor hemorrhage, edema, or an inaccurate evaluation of size change. We used this approach clinically with two patients (unpublished data). Both patients had large posterior uveal melanomas in their only eyes, which had been treated elsewhere with radiation; they were referred for management of recurrent tumor growth. In one case a fine needle biopsy demonstrated no cells in the DNA synthesis phase on the basis of bromodeoxyuridine stains. After 15 months of follow-up, there has been no change in tumor size. The second case demonstrated

bromodeoxyuridine-positive cells on fine needle biopsy. The enucleated tumor showed numerous mitoses.

There are a number of other potential ramifications of these types of studies. In some malignancies, response to either radiation or chemotherapy has correlated with the number of cells in synthesis and the degree of DNA aneuploidy.[36,37] These data might be important in treatment planning.

Similarly, the wide range of regression patterns after uveal melanoma irradiation may partially reflect differences in the cell cycle status. Possibly, some uveal melanomas could be treated with less radiation, on the basis of their DNA content or number of cells in DNA synthesis with less resultant ocular morbidity. It is also possible to estimate cell doubling time using a single injection of bromodeoxyuridine.[38,39]

Bromodeoxyuridine labeling, as a measure of the DNA synthesis phase of the tumor cell cycle, was relatively low (1% to 8%) in nonirradiated uveal melanomas in this study; these data imply a relatively slow doubling rate for this tumor. These results are consistent with other reports in which epithelial or entodermal malignancies appear to have a higher DNA synthesis rate than most mesenchymal neoplasms, such as sarcomas or neuroectodermally derived melanomas.[40,41]

There are a number of potential limitations to bromodeoxyuridine assays. Our studies do not address all of them. First, there are some theoretic and actual limitations of bromodeoxyuridine assessment of the synthesis phase. Bromodeoxyuridine may not be uniformly incorporated into DNA during the entire synthesis phase of the cell cycle.[42] DNA synthesis can occur outside of the synthesis phase during repair of sublethal damage as a result of either radiation or chemotherapy.[42] In some neoplasms, it is difficult to determine whether failure of bromodeoxyuridine incorporation is because of absence of DNA synthesis or unavailability of bromodeoxyuridine either as a result of poor vascular supply to the tumor or limited tissue diffusion.[25]

A major problem with flow cytometric analysis of the synthesis phase, and the predominant reason we chose to base our studies on the fluorescent microscopy data, is that nontumor cells infiltrating a malignancy are also stained with bromodeoxyuridine if they are cycling.[31,43] While inflammatory cell infiltration into uveal melanomas is uncommon, it does occur. Unless three-channel flow cytometry is performed with a different fixation technique and additional labeled monoclonal antibodies directed toward antigens on lymphocytes and monocytes, microscopy is needed to screen out bromodeoxyuridine uptake by nontumor cells.[44,45]

Finally, the accuracy of bromodeoxyuridine uptake as a measure of radiation destruction of a tumor's reproductive integrity relies upon appropriate sampling. At radiation doses of 20 Gy or more, over 99% of the tumor cells are probably sterilized.[1] In studies of uveal melanoma cells performed 48 hours after receiving 20 Gy of preenucleation radiation, probably less than 1% can potentially cycle, and some of these cells may be temporarily arrested in the cell cycle.[1] It is difficult to determine if this small number of cells were either sampled or reflected permanent vs transient damage at the time of study. It is conceivable that if the interval between 20-Gy photon irradiation and enucleation were increased to several months, the presumed 1% of cells that may have retained reproductive integrity could have reexpanded, and a number of these might have stained with bromodeoxyuridine. We have clinically and histologically examined two uveal melanomas treated elsewhere with 30 Gy of photon irradiation because of an incorrect diagnosis of choroidal metastases that showed renewed tumor growth within one year of treatment, presumably on this basis. The results observed in the melanomas treated with helium ions should accurately reflect destruction of tumor reproductive integrity. These neoplasms were enucleated, on the average, over two years after radiation without evidence of tumor reactivation. In all cases, multiple sections failed to demonstrate bromodeoxyuridine uptake.

The morbidity of in vivo bromodeoxyuridine studies appears to be minimal. At our institution, we have studied over 150 patients with various types of malignancies using this agent with no obvious side effects.[29,46] The mean plasma concentration of this agent is 8 μM two hours after treatment. Further, there are a number of previous studies in which bromodeoxyuridine was given in much higher doses for up to several weeks at a time as a radiation sensitizer. In these studies, there was no permanent morbidity.[15,46,47] This approach may be useful in increasing our understanding of the biologic activity as well as the management of uveal melanomas and other intraocular and orbital tumors.

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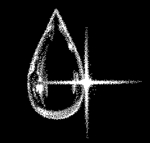

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CONTRAINDICATIONS: TIMOPTIC is contraindicated in patients with bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease (see WARNINGS); sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; hypersensitivity to any component of this product.

WARNINGS: As with other topically applied ophthalmic drugs, this drug may be absorbed systemically.

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and, rarely, death in association with cardiac failure, have been reported following administration of TIMOPTIC (see CONTRAINDICATIONS).

Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, TIMOPTIC should be discontinued.

Obstructive Pulmonary Disease: PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (e.g., CHRONIC BRONCHITIS, EMPHYSEMA) OF MILD OR MODERATE SEVERITY, BRONCHOSPASTIC DISEASE OR HISTORY OF BRONCHOSPASTIC DISEASE (OTHER THAN BRONCHIAL ASTHMA OR HISTORY OF BRONCHIAL ASTHMA, IN WHICH 'TIMOPTIC' IS CONTRAINDICATED, see CONTRAINDICATIONS), SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS, INCLUDING 'TIMOPTIC'. However, if TIMOPTIC is necessary in such patients, then the drug should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery: The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine, or levarterenol.

Diabetes Mellitus: Beta-adrenergic blocking agents should be administered with caution to patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents which might precipitate a thyroid storm.

PRECAUTIONS: *General:* Patients who are receiving a beta-adrenergic blocking agent orally and TIMOPTIC should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

Patients should not receive two topical ophthalmic beta-adrenergic blocking agents concurrently.

Because of potential effects of beta-adrenergic blocking agents relative to blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with TIMOPTIC, alternative therapy should be considered.

Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. TIMOPTIC has little or no effect on the pupil. When TIMOPTIC is used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be used with a miotic and not alone.

As with the use of other antiglaucoma drugs, diminished responsiveness to TIMOPTIC (Timolol Maleate, MSD) after prolonged therapy has been reported in some patients. However, in one long-term study in which 96 patients have been followed for at least three years, no significant difference in mean intraocular pressure has been observed after initial stabilization.

Drug Interactions: Although TIMOPTIC used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with TIMOPTIC and epinephrine has been reported occasionally.

Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Caution should be used in the coadministration of beta-adrenergic blocking agents, such as TIMOPTIC, and oral or intravenous calcium antagonists, because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided.

The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

Animal Studies: No adverse ocular effects were observed in rabbits and dogs administered TIMOPTIC topically in studies lasting one and two years respectively.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year oral study of timolol maleate in rats, there was a statistically significant ($p \leq 0.05$) increase in the incidence of adrenal pheochromocytomas in male rats administered 300 times the maximum recommended human oral dose* (1 mg/kg/day). Similar differences were not observed in rats administered oral doses equivalent to 25 or 100 times the maximum recommended human oral dose. In a lifetime oral study in mice, there were statistically significant ($p \leq 0.05$) increases in the incidence of benign and malignant pulmonary tumors and benign uterine polyps in female mice at 500 mg/kg/day, but not at 5 or 50 mg/kg/day. There was also a significant increase in mammary adenocarcinomas at the 500-mg/kg/day dose. This was associated with elevations in serum prolactin which occurred in female mice administered timolol at 500 mg/kg, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in man. Furthermore, in adult human female subjects who received oral dosages up to 60 mg timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

There was a statistically significant increase ($p \leq 0.05$) in the overall incidence of neoplasms in female mice at the 500-mg/kg/day dosage level.

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 μg/mL). In Ames tests, the highest concentrations of timolol employed, 5000 or 10,000 μg/plate, were associated with statistically significant elevations ($p \leq 0.05$) of revertants observed with tester strain TA100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, nor did the ratio of test to control revertants reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses up to 150 times the maximum recommended human oral dose.

Pregnancy: Pregnancy Category C: Teratogenicity studies with timolol in mice and rabbits at doses up to 50 mg/kg/day (50 times the maximum recommended human oral dose) showed no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (1,000 times the maximum recommended human oral dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 100 times the maximum recommended human oral dose, in this case without apparent maternotoxicity. There are no adequate and well-controlled studies in pregnant women. TIMOPTIC should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established by adequate and well-controlled studies.

ADVERSE REACTIONS: TIMOPTIC Ophthalmic Solution is usually well tolerated. The following adverse reactions have been reported either in clinical trials of up to three years' duration prior to release in 1978 or since the drug has been marketed.

BODY AS A WHOLE: Headache, asthenia, chest pain. CARDIOVASCULAR: Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, palpitation, cardiac arrest. DIGESTIVE: Nausea, diarrhea. NERVOUS SYSTEM/PSYCHIATRIC: Dizziness, depression, increase in signs and symptoms of myasthenia gravis, paresthesia. SKIN: Hypersensitivity, including localized and generalized rash, urticaria. RESPIRATORY: Bronchospasm (predominantly in patients with preexisting bronchospastic disease), respiratory failure, dyspnea, nasal congestion. ENDOCRINE: Masked symptoms of hypoglycemia in insulin-dependent diabetics (see WARNINGS). SPECIAL SENSES: Signs and symptoms of ocular irritation, including conjunctivitis, blepharitis, keratitis, blepharoptosis, decreased corneal sensitivity, visual disturbances, including refractive changes (due to withdrawal of miotic therapy in some cases), diplopia, ptosis.

Causal Relationship Unknown: The following adverse effects have been reported, and a causal relationship to therapy with TIMOPTIC has not been established: *Body as a Whole:* Fatigue; *Cardiovascular:* Hypertension, pulmonary edema, worsening of angina pectoris; *Digestive:* Dyspepsia, anorexia, dry mouth; *Nervous System/Psychiatric:* Behavioral changes including confusion, hallucinations, anxiety, disorientation, nervousness, somnolence, and other psychic disturbances; *Skin:* Alopecia; *Special Senses:* Aphakic cystoid macular edema; *Urogenital:* Retroperitoneal fibrosis, impotence.

The following additional adverse effects have been reported in clinical experience with oral timolol maleate and may be considered potential effects of ophthalmic timolol maleate: *Body as a Whole:* Extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular:* Edema, worsening of arterial insufficiency, Raynaud's phenomenon, vasodilatation; *Digestive:* Gastrointestinal pain, hepatomegaly, vomiting; *Hematologic:* Nonthrombocytopenic purpura; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Pruritus, skin irritation, increased pigmentation, sweating, cold hands and feet; *Musculoskeletal:* Arthralgia, claudication; *Nervous System/Psychiatric:* Vertigo, local weakness, decreased libido, nightmares, insomnia, diminished concentration; *Respiratory:* Rales, cough, bronchial obstruction; *Special Senses:* Tinnitus, dry eyes; *Urogenital:* Urination difficulties.

Potential Adverse Effects: In addition, a variety of adverse effects have been reported with other beta-adrenergic blocking agents and may be considered potential effects of ophthalmic timolol maleate: *Digestive:* Mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* Agranulocytosis, thrombocytopenic purpura; *Nervous System:* Reversible mental depression progressing to catatonia; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Allergic:* Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; *Urogenital:* Peyronie's disease.

There have been reports of a syndrome comprising psoriasiform skin rash, conjunctivitis sicca, otitis, and sclerosing serositis attributed to the beta-adrenergic receptor blocking agent practolol. This syndrome has not been reported with timolol maleate.

HOW SUPPLIED: TIMOPTIC Ophthalmic Solution, 0.25% and TIMOPTIC Ophthalmic Solution, 0.5%. Both are available in 2.5-mL, 5-mL, 10-mL, and 15-mL plastic OCUMETER® ophthalmic dispensers with a controlled drop tip. **Also Available:** Preservative-free TIMOPTIC in OCUDOSE® (Dispenser) Sterile Ophthalmic Unit-Dose Dispenser (see separate Prescribing Information).

Storage: Protect from light. Store at room temperature.

*The maximum recommended single oral dose is 30 mg of timolol. One drop of TIMOPTIC 0.5% contains about 1/150 of this dose, which is about 0.2 mg.

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For more detailed information, consult your MSD Representative and the Prescribing Information.
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J8TM28 (426/303)

Contralateral Trochlear Nerve Paresis and Ipsilateral Horner's Syndrome

John Guy, M.D., Arthur L. Day, M.D., J. Parker Mickle, M.D., and Norman J. Schatz, M.D.

Two patients had paresis of the trochlear nerve contralateral to the site of lesions in the brainstem. Both patients had ipsilateral blepharoptosis and miosis suggesting oculosympathetic paresis from involvement of the descending sympathetic tract, adjacent to the fourth cranial nerve nucleus and its fascicles, in the caudal mesencephalon. Cerebral angiography documented an arteriovenous malformation of the brainstem in Case 1. Magnetic resonance imaging disclosed a lesion of high signal intensity on T_2-weighted images involving the dorsal mesencephalon in Case 2. Involvement of the superior cerebellar peduncle produced ipsilateral dysmetria and ataxia. Lesions involving the fourth cranial nerve nucleus or its fascicles, before decussation in the superior medullary velum, and adjacent sympathetic fibers may produce an ipsilateral Horner's syndrome and contralateral superior oblique muscle paresis.

THE CLINICAL SYNDROME of diplopia associated with Horner's syndrome usually suggests anatomic localization of the lesion to the ipsilateral orbital apex, superior orbital fissure, or cavernous sinus.[1] Intrinsic brainstem dysfunction may be associated with skew deviation or supranuclear, internuclear, nuclear, or fascicular causes for the diplopia.[1,2]

In 1983 Coppeto[3] pointed out that superior oblique muscle paresis contralateral to the eye with a Horner's syndrome was a localizing sign of a caudal lesion of the dorsal mesencephalon. Although this clinical syndrome is uncommon,[3-9] we encountered two such cases.

Accepted for publication Oct. 24, 1988.

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Case Reports

Case 1

A 29-year-old woman complained of right hemicranial headache, left hemibody weakness, and binocular diplopia. On examination, visual acuity was 20/20 in each eye. There was 1 mm of right blepharoptosis. In dim illumination the right pupil measured 3.5 mm and the left pupil 4.5 mm. In bright illumination they both measured 3 mm. Cocaine testing produced no dilation of the right pupil, but the left pupil increased to 6.5 mm, confirming a right oculosympathetic paresis. Motility examination disclosed an 8-prism diopter left hypertropia in primary gaze that increased to 10 prism diopters in right lateral gaze, but decreased to 2 prism diopters in left lateral gaze. With right head tilt the left hypertropia was absent, but increased to 14 prism diopters in left head tilt, consistent with paresis of the left trochlear nerve. There was 5 degrees of excyclodeviation of the left globe. There was also 5 prism diopters of esotropia in primary position that increased to 10 prism diopters in right lateral gaze, but was absent in left lateral gaze, suggesting mild paresis of the right abducens nerve. Results of Goldmann visual field testing and ophthalmoscopy of the optic nerve heads were normal.

Neurologic examination demonstrated hypesthesia in the distribution of the right trigeminal nerve and a left central facial nerve paresis, in addition to the right Horner's syndrome and right sixth and left fourth cranial nerve pareses. A left hemiparesis, marked dysmetria of

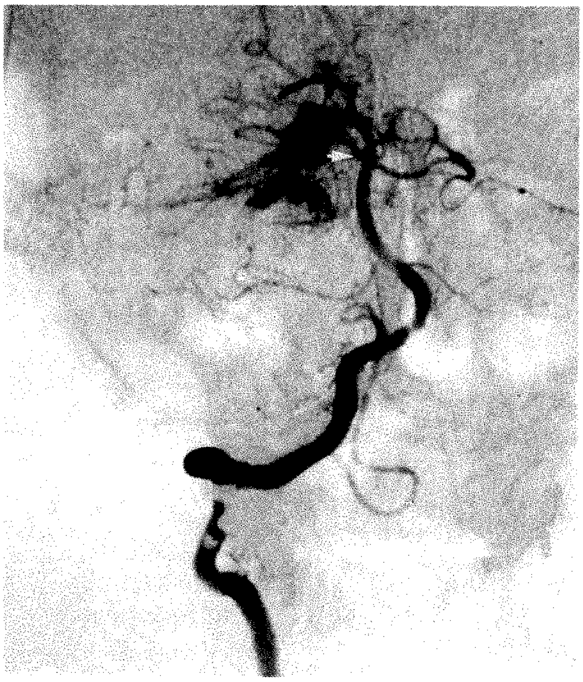

Fig. 1 (Guy and associates). Case 1. Right vertebral angiogram showing right-sided brainstem arteriovenous malformation, fed by the superior cerebellar artery (arrow), in anteroposterior view.

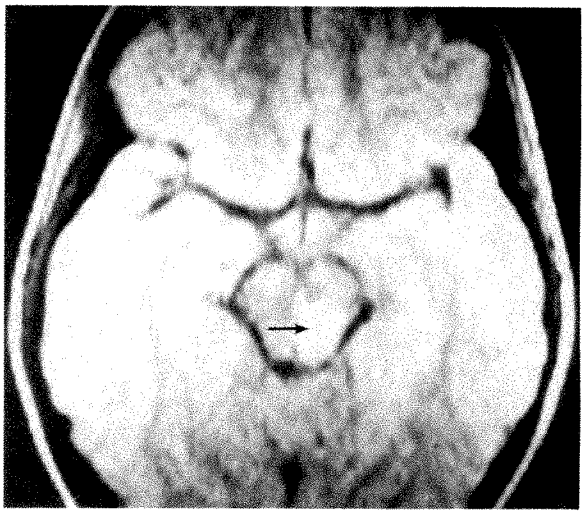

Fig. 2 (Guy and associates). Case 2. Magnetic resonance imaging shows lesion (arrow) in left dorsal midbrain on T_2-weighted image.

the right upper extremity, and truncal ataxia were also present.

Cerebral angiography demonstrated an arteriovenous malformation involving the right lower mesencephalon, supplied by the superior cerebellar artery (Fig. 1).

Case 2

An 11-year-old boy complained of binocular vertical diplopia for one week. Three days before admission his parents noted that the right pupil was larger than the left. On examination, visual acuity was 20/20 in each eye. There was 0.5 mm of left blepharoptosis. The right pupil measured 5 mm and the left pupil 3 mm. In dim illumination the anisocoria increased to 7 mm on the right and 3 mm on the left, compatible with left oculosympathetic paresis. Motility measurements showed orthotropia in primary position and in right lateral gaze, but an 8-prism diopter right hypertropia was present in left lateral gaze. With right head tilt there was 10 prism diopters of right hypertropia, which was absent on left head tilt, consistent with a right fourth cranial nerve paresis. Results of ophthalmoscopy of the optic nerve heads were normal. Neurologic examination disclosed mild left upper extremity dysmetria and difficulty with tandem gait, in addition to the right fourth cranial nerve paresis and left Horner's syndrome.

Magnetic resonance imaging demonstrated a lesion involving the left dorsal midbrain, on T_2-weighted images (Fig. 2). Cerebral angiography showed the lesion to be avascular and without mass effect. A lumbar puncture was slightly traumatic, with 272 red blood cells. Cerebrospinal fluid analysis was otherwise normal with five mononuclear leukocytes, a protein level of 19 mg/dl, a glucose level of 77 mg/dl, and IgG <1.2 mg/dl. Brainstem auditory-evoked potentials were normal. Symptoms resolved after three months.

Discussion

Our two patients had ipsilateral Horner's syndrome and superior oblique muscle paresis, contralateral to lesions of the brainstem. The criteria necessary for diagnosis of fourth cranial nerve paresis, established by the three-step test,[4,7,8] were satisfied by the motility measurements of both patients. A lesion involving the trochlear nucleus, or its fascicles, may result in contralateral paresis of the superior oblique muscle.[3,10] In both cases neuro-imaging of the upper brainstem demonstrated a discrete lesion in the region of the trochlear nucleus and fascicular fibers of the fourth cranial nerve before decussation in the superior medullary

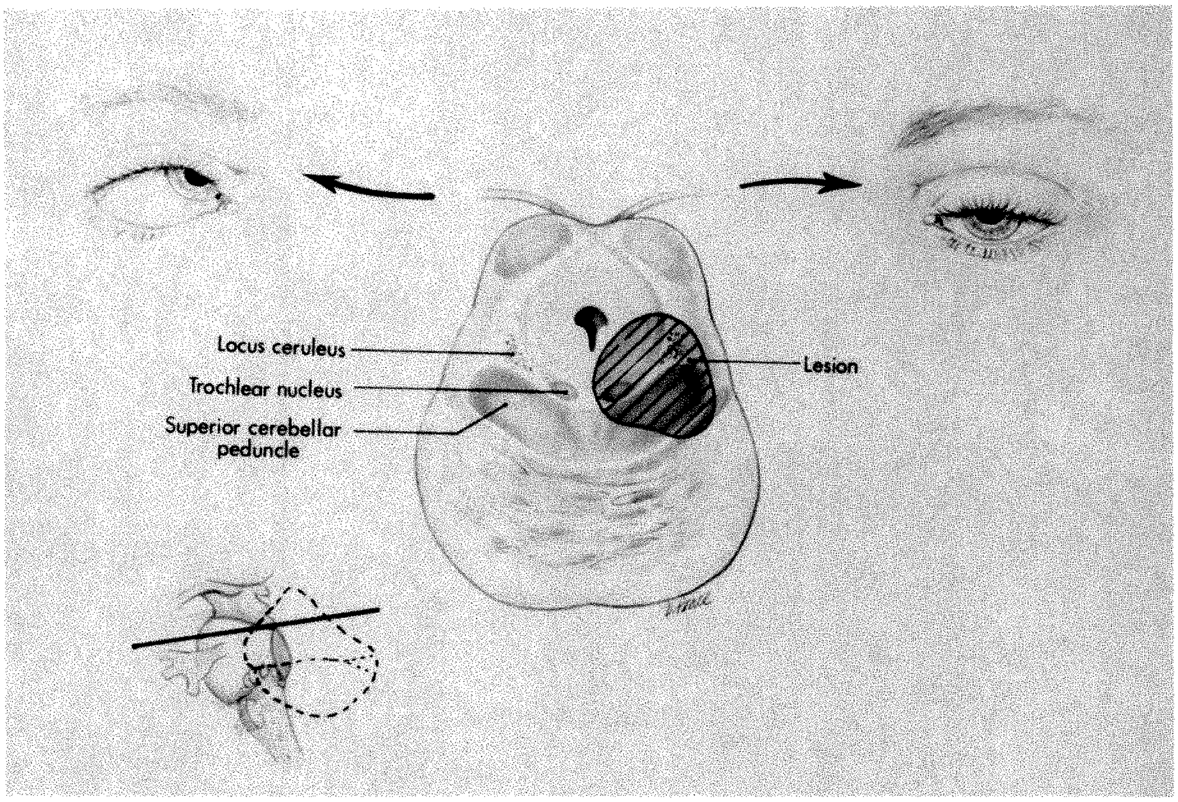

Fig. 3 (Guy and associates). Illustration of the caudal mesencephalon at the level of the fourth cranial nerve nucleus and superior medullary velum. A lesion of the left side producing right hypertropia (overaction of the right inferior oblique muscle is shown), resulting from involvement of the trochlear nucleus or fascicles, and left blepharoptosis from interruption of the adjacent descending sympathetic pathway. Ventrolateral extension of the lesion to the superior cerebellar peduncle may produce ipsilateral dysmetria and truncal ataxia.

velum and the descending sympathetic pathway (Fig. 3).

Anisocoria greater in dim than bright illumination and the presence of blepharoptosis was suggestive of oculosympathetic paresis in both patients, which was confirmed on cocaine testing in Case 1. While the precise anatomic localization of the descending ocular sympathetic pathway in the brainstem is uncertain, it may involve the noradrenergic nucleus locus ceruleus, which is in close proximity to the trochlear nucleus in the dorsolateral tegmentum.[10] The cerebellar signs in our patients were the result of involvement of the adjacent superior cerebellar peduncle, which occupies a ventrolateral position at this level (Fig. 3).

Skew deviation may be a cause of hypertropia with lesions involving this area of the brain.[11-13] However, in our patients the motility pattern and positive head tilt correlated best with paresis of the trochlear nerve.[4,8]

Paresis of the fourth cranial nerve may occur with lesions of the brainstem including glioma,[14] metastatic carcinoma,[15] arteriovenous malformation,[16,17] hydrocephalus,[18] and multiple sclerosis.[5-7,16] However, the presence of paresis of the superior oblique muscle contralateral to the eye with Horner's syndrome was first described by Coppeto.[3]

Isolated paresis of the trochlear nerve may require little neurodiagnostic investigation.[19] The presence of Horner's syndrome contralateral to the eye with superior oblique muscle paresis suggests a caudal lesion of the dorsal mesencephalon. Patients with this clinical syndrome should have neuro-imaging studies directed to this anatomic site.

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AMERICAN JOURNAL OF OPHTHALMOLOGY®

FRANK W. NEWELL, *Publisher and Editor-in-Chief*
Suite 1415, 435 North Michigan Ave., Chicago, Illinois 60611

Published monthly by the OPHTHALMIC PUBLISHING COMPANY
Suite 1415, 435 North Michigan Avenue, Chicago, Illinois 60611

PERSPECTIVES

The Expanding Ophthalmologic Spectrum of Lyme Disease

Thomas M. Aaberg, M.D.

LYME DISEASE, now established as an immune-mediated multisystem disorder, was so named in 1975 because of an unusual clustering of children with inflammatory arthropathy in Lyme, Connecticut.[1] The clinical hallmark, a distinctive expanding skin lesion erythema chronicum migrans, follows the bite of Ixodidae ticks, described at the beginning of this century.[2] In the United States three distinct foci of Lyme disease follow the distribution of *Ixodes dammini* in the northeast and upper midwest and *Ixodes pacificus* in the west,[3] although other tick vectors have been reported over large geographic areas within the continental United States. The spirochete *Borrelia burgdorferi*, transmitted by the Ixodidae ticks, is recognized as the cause of Lyme disease, which has now become the most common tick-transmitted illness in the United States.[4] Clinical similarities between the illnesses in Europe and the United States, as well as similar spirochetes recovered from infected ticks, documented a common identity in the two continents. However, the disease in this country, as contrast to the manifestations in Europe, disseminates more rapidly creating joint, neurologic, or cardiac abnormalities.[2]

See also p. 81.

Ophthalmologists should become familiar with the manifestations of Lyme disease since patients may have ocular disorders in any stage of the disease. If recent literature is an indication, the number of future patients with Lyme disease-related eye disorders will increase significantly.[5-8]

Stages of Lyme Disease

Three clinical stages of Lyme disease have been demonstrated. Stage 1, or early disease, includes constitutional flu-like symptoms.[2] During this period of dissemination, some patients develop dermatologic findings not associated with previous tick bite. Conjunctivitis, the most common reported ocular complication

of Lyme disease,[2,9] may occur during Stage 1, thus involving the ophthalmologist in the early manifestations of the disease.

IgM anti-*B. burgdorferi* antibody increase occurs during this early stage and is the first immunologic response, reaching a maximum by three to six weeks. However, a delayed IgM response to a specific *B. burgdorferi* antigen may occur several months to a year after infection.[10] IgG anti-*B. burgdorferi* antibody appears later, becoming the dominant delayed antibody response as IgM anti-*B. burgdorferi* antibody levels wane. Increasing titers of IgM anti-*B. burgdorferi* antibodies and cryoglobulins in the early disease appear to be prognostic harbingers of Stage 2 or Stage 3 disease. Subsequently, patients with either Stage 2 or Stage 3 are uniformly positive for IgG anti-*B. burgdorferi* antibody.[11] Based on the reported increased IgM anti-*B. burgdorferi* antibody level, the case of bilateral diffuse choroiditis and exudative retinal detachment reported by Bialasiewicz and associates,[6] apparently represents an ocular manifestation of Stage 1 or early Stage 2 disease. Other ocular manifestations, including iridocyclitis and retinal vasculitis, have been reported in these early stages. During the ensuing stage of dissemination when central nervous system signs appear, decreased vision may lead to ophthalmologic consultation. Wu and associates[7] described a patient with a markedly increased IgM anti-*B. burgdorferi* antibody titer, indicating an early stage of Lyme disease, with optic disk edema and macular edema. In view of the normal cerebral spinal fluid pressure, their patient appears to have had optic perineuritis and associated macular edema. A similar ocular manifestation with disk edema was reported by Reik and associates[12] in four of their five patients.

A second cause of optic disk edema, pseudotumor cerebri associated with Lyme disease, is illustrated by the case described by Jacobson and Frens, in this issue of THE AMERICAN JOURNAL OF OPHTHALMOLOGY. Additional cases have been reported by Raucher and associates[13] as well as one of the cases of Reik and associates.[12]

Stage 2 Lyme disease involves cardiac and neurologic disease. While symptoms suggestive of meningeal irritation may occur at the beginning of the illness, with episodic attacks of excruciating headache and neck pain, about 15% of patients develop more significant neurologic abnormalities as a manifestation of Stage 2 after several weeks to months of the disease. A common triad of symptoms consists of meningitis, radiculoneuropathy, and cranial neuropathy, including Bell's palsy or, less frequently, paresis of the third or sixth cranial nerves. The *B. burgdorferi* spirochete has been recovered from cerebral spinal fluid,[14] as well as spirochetal forms from the vitreous,[15] during Stage 2 infection. Thus, the ophthalmologist is again involved in the diagnosis and treatment of Lyme disease victims at another stage of the disease.

Cardiac involvement occurs early in Stage 2 within several weeks of illness onset in about 8% of patients.[16] Fluctuating degrees of atrioventricular block are most common but some patients have evidence of diffuse cardiac disease including acute myopericarditis or, rarely, cardiomegaly. The symptoms are similar to those of acute rheumatic fever, although in Lyme disease heart block is more common and the cardiac valves are not affected.[2] The origin has been verified by recovering spirochetes from cardiac tissue during this stage.[17]

A patient with bilateral keratitis involving epithelial basement membrane, superficial and deep corneal stroma during delayed Stage 2 or early Stage 3 disease was described by Baum and associates.[5] If substantiated by future experience, this unusual form of keratitis may cause ophthalmologists to be suspicious of Lyme disease when prodromal disease is not apparent.

The late manifestations of Lyme disease, Stage 3, are characterized by arthritis and chronic neurologic syndromes. Within a few weeks to two years after infection approximately 60% of afflicted patients develop arthritis.[18] When arthropathy develops early, the pattern is that of migratory pain in joints, tendons, bursae, muscle, or bone, often without joint effusion, and lasting a few hours to several days at a given location.[2] Definite arthritis with marked joint effusion does not begin for months after infestation with the *Borrelia* spirochete, afflicting large joints, particularly the knee. In about 10% of patients with Lyme arthritis, the involvement of large joints persists chronically with erosion of cartilage and bone.[19]

Patients with Stage 3 late neurologic manifestations, including neuropsychiatric disease, fatigue syndromes, or focal central-nervous-system disease may complain of decreased vision or diplopia. While these same ocular symptoms may occur in the early disease stages, the symptoms have a longer duration in the chronic stage. Persistent neurologic disease with progressive deterioration as a tertiary manifestation of persistent spirochetal infection of the central nervous system has been

postulated by Broderick, Sandok, and Mertz.[20] Their patient was asymptomatic, after classic acute Lyme disease, until developing signs of progressive focal encephalitis six years later, which responded to penicillin therapy without other identifiable infectious agents. Considerable variation may thus occur in the clinical expression of Lyme disease, possibly even in ophthalmic expression. Furthermore, the development of severe and prolonged illness has been associated with genetic susceptibility manifest as an increased frequency of the B-cell alloantigen DR2 as compared to patients with mild disease.[18]

Diagnosis of Lyme Disease

The diagnosis of Lyme disease requires persistent clinical consideration. The sensitivities of the indirect immunofluorescent antibody and enzyme-linked immunosorbent assay (ELISA) are relatively low during Stage 1. Additionally, a curtailment of antibody response may occur after early antibiotic treatment.[21,22] By Stages 2 and 3 sensitivities greater than 95% have been reported,[11,12] even approaching 100%.[23] Of the two available serologic tests, the ELISA method is favored because of the higher levels of sensitivity and specificity.[21] Because previous reports of the serologic testing have been variable in the reported sensitivities without adequate standardization, the Centers for Disease Control advise against the use of serologic testing alone for routine disease reporting and emphasize the need for a reliable and practical case surveillance definition that combines clinical signs and serologic testing.[24] The diagnostic criteria for definite Lyme disease diagnosis from the Centers for Disease Control are summarized in the Table.

Serologic testing is currently most beneficial in patients without a history of typical skin rash or who have neurologic, cardiac, joint, or ophthalmologic disorders.[16] Serial IgM anti-*B. burgdorferi* antibody levels, if increased, remain the best laboratory indicator of Lyme disease but may be equivocal at this stage. Increased serial IgM anti-*B. burgdorferi* antibody levels are reliable prognostic indicators, however, of impending staged progression.

Treatment of Lyme Disease

In early disease oral antibiotic therapy shortens the duration of systemic symptoms and prevents development of delayed disease in most patients. A summary of treatment regimens for Lyme disease has recently been published.[25] Non-pregnant women, other adults, and children over 8 years of age require 250 mg of oral tetracycline four times daily or 100 mg of doxycycline twice daily for ten days to three weeks. Penicillin V or amoxicillin in pediatric doses are also effective for children. Patients with mild neurologic manifestations (such as Bell's palsy) respond to the same tetracycline or doxycycline regimen but treatment must be continued for up to a month. Severe neurologic or cardiac disease requires intravenous penicillin G, 20 million units daily for ten to 14 days. Ceftriaxone is prescribed in nonresponsive cases, but only with variable success in Stage 3 neurologic disease. Penicillin G, given intravenously for two to three weeks, has been effective for Lyme arthritis although the response may be delayed for weeks or months.[26]

All stages of Lyme disease have been found to respond to antibiotic treatment. The determination of the best regimen for various stages and organ expression awaits controlled trials.[25]

Recent surveillance studies have demonstrated that Lyme disease is spreading among individuals within endemic areas as well as to other geographic areas. In Connecticut, where parasitism of ticks by the spirochete *B. burgdorferi* is approximately 60%,[16] the incidence of Lyme disease for all Connecticut residents in 1985 was 22/100,000 while town-specific incidences ranged from zero to 1,156/100,000.[24] Compared to statistics published in a 1977 report, this is an increase of 163% in Lyme disease in the eight towns reporting cases. It was also apparent the disease has now spread inland from the coastal areas. The organism has now been isolated in most of the continental United States. Thus, ophthalmologists must maintain a constant level of clinical awareness with patients who have unusual forms of conjunctivitis, keratitis, iridocyclitis, retinal vasculitis, or disk edema and who have been within endemic areas. Fortunately, response to therapy is usual

TABLE
DIAGNOSTIC CRITERIA FOR LYME DISEASE*

AREA	CRITERIA
Endemic	1. Erythema migrans with exposure no more than 30 days prior to onset
	2. Involvement of ≥ one organ system† and a positive antibody test
Nonendemic	1. Erythema migrans with positive antibody test
	2. Erythema migrans with involvement of ≥ two organ systems†

*Adapted from Duffy, J.[16]
†Musculoskeletal, neurologic, or cardiac.

and satisfactory when the disease is discovered in the early stages.

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LETTERS TO THE JOURNAL

Pseudotumor Cerebri Syndrome Associated With Lyme Disease

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Neuro-ophthalmic complications of Lyme disease are being recognized with greater frequency as experience with this disorder increases. Reported associations include uveitis, chorioretinitis, interstitial keratitis, optic neuritis, ischemic optic neuropathy, and ocular motor nerve palsies. Some authors have assumed a cause and effect relationship between Lyme disease and ophthalmic disorders on the basis of a positive Lyme titer only. Such cases may represent spurious associations because the prevalence of asymptomatic seropositivity is undefined in many regions. The following case illustrates another neuro-ophthalmic manifestation in an individual with characteristic clinical features of Lyme disease.

See also p. 77.

An 8-year-old girl from central Wisconsin was bitten by a tick in July 1987. In late August she developed fever, headaches, lethargy, and

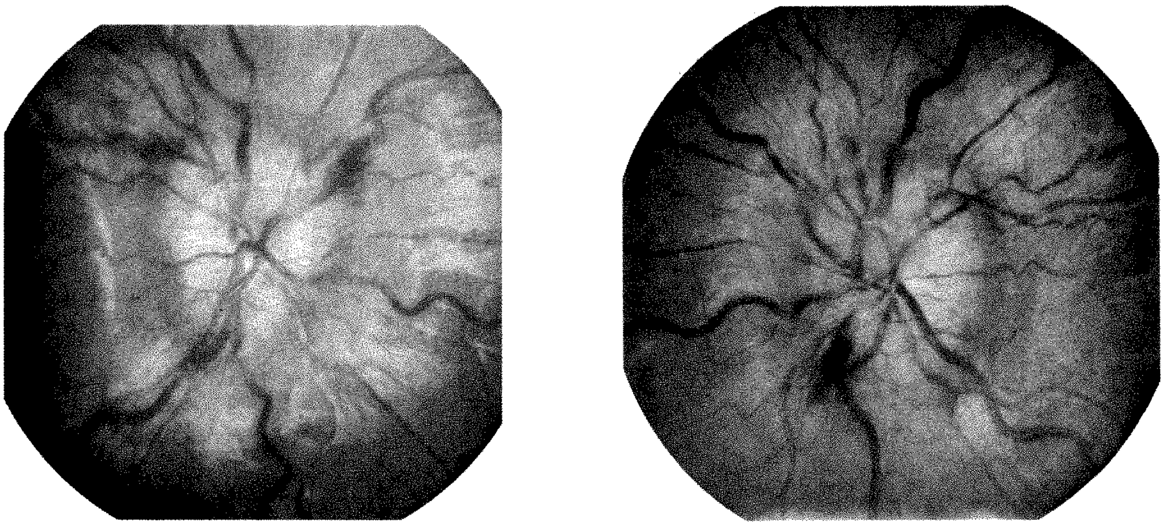

Fig. 1 (Jacobson and Frens). Swollen optic disk of the right eye (left) and left eye (right) at the time of diagnosis.

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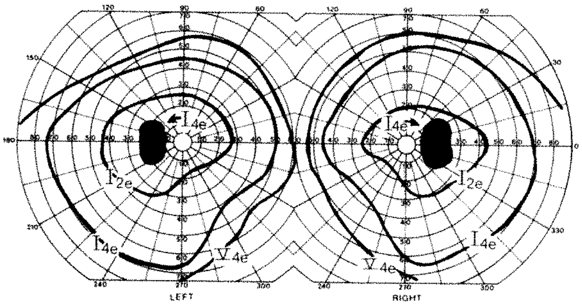

Fig. 2 (Jacobson and Frens). Initial visual field showing bilateral blind spot enlargement and inferonasal defects.

intermittent diplopia. A red rash with a surrounding ring was noted on the child's thigh. Results of a Lyme titer obtained on Sept. 3 were normal. She was treated with oral penicillin for ten days. All symptoms resolved within a few days of therapy.

On Oct. 12, she developed myalgias, headaches, red eyes, photophobia, neck pain, and diplopia. Results of another Lyme titer were normal. All symptoms resolved during the next week except the diplopia.

When examined on Oct. 21, results of the patient's general medical and neurologic examinations were normal. Visual acuity was 20/20 in each eye. Color vision, pupil reactions, and anterior segments were all normal. Bilateral optic disk edema was noted (Fig. 1). Visual fields showed bilateral blind spot enlargement and inferonasal loss (Fig. 2). She had full ductions with 18 prism diopters of esotropia in forward gaze that decreased to 14 prism diopters in right and left gaze.

Results of computed tomography of the head were normal. Results of routine laboratory studies and viral studies were normal. Lyme titer was 1:512 (normal, >1:256). Cerebrospinal fluid analysis showed an opening pressure greater than 360 mm Hg, 97 white blood cells/ml^3 (69% lymphocytes, 30% monocytes), a protein level of 28 mg/dl, and negative microbiologic studies.

She was treated with a 14-day course of intravenous ceftriaxone. When seen in follow-up on Dec. 12, she had no symptoms. Her visual acuity was 20/20 in each eye and she showed complete resolution of the papilledema and the previously noted visual field abnormalities. Ocular motility was normal.

As demonstrated by this case, Lyme disease should be considered in the differential diagnosis of pseudotumor cerebri syndrome in endemic areas; Lyme titers may be normal early in the course of illness, or may be suppressed by antibiotic therapy, so that serial determinations should be performed in suspected cases; and central nervous system and neuro-ophthalmic manifestations are protean and may spontaneously undergo exacerbation and remission.

Bilateral optic disk edema associated with Lyme disease could result from either papilledema or optic perineuritis. Our case and those reported by Raucher and colleagues[1] exemplify the former mechanism. Although not recognized as such, optic perineuritis was probably the cause of optic disk edema observed in the patients described by Wu and associates[2] and Reik and associates[3] who had normal cerebrospinal fluid pressure and meningitis.

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Magnetic Resonance Imaging of Retrobulbar Changes in Optic Nerve Position With Eye Movement

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Several recent articles have reported that brainstem anesthesia with respiratory depression, seizures, or ipsilateral (or contralateral) cranial nerve deficits can occur as a rare compli-

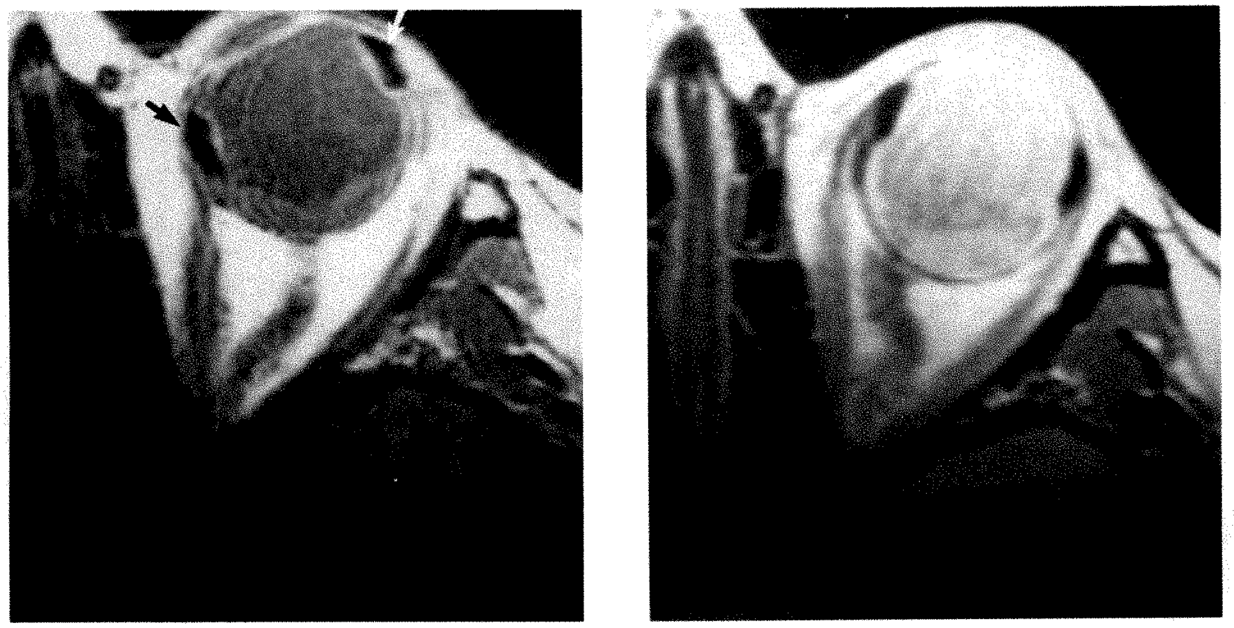

Figure (Smiddy, Michels, and Kumar). Left, Magnetic resonance image of eye with retinal detachment rotated superonasally. The retrobulbar segment of the optic nerve is taut and displaced laterally. This patient had undergone a previous scleral buckling operation, and the broad, hard silicone explant is visible (arrows). Right, The same eye in primary position. The retrobulbar segment of the optic nerve is loosely coiled and located more nasally.

cation of retrobulbar anesthetic injection.[1-3] This is presumed to be caused by injection of the anesthetic agent beneath the dura of the optic nerve, thus introducing the drug within the subarachnoid space surrounding the brainstem.[1] Recent anatomic studies[4] and clinical series[1,3] have suggested that the optic nerve is displaced temporally when the eye is rotated superonasally and that this may increase the risk of damage by a retrobulbar needle introduced inferotemporally.

We performed magnetic resonance imaging on three patients with retinal detachments to assess the position of the retrobulbar portion of the optic nerve. When the eye was rotated superonasally, the retrobulbar segment of the optic nerve was taut and displaced laterally (Figure). In primary position, the retrobulbar segment was more medial and coiled in a loose, redundant configuration. Because the eye rotates about an axis of Fick, the position of the most posterior portion of the globe relative to the adjacent orbital tissues was not substantially different in either position of gaze. Therefore, the risk of needle damage to the globe did not seem to be altered by changing the position of gaze.

These findings have caused us to alter our technique for retrobulbar anesthetic injection. The injection is given in the inferotemporal quadrant with the eye in primary position rather than directed superonasally.

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Discordance of Accommodative Esotropia in Monozygotic Twins

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As early as the 19th century, Donders[1] emphasized hyperopia as the most important factor in the origin of accommodative esotropia. Conversely, Worth believed that an inherited defect in the fusional facility was the essential cause of strabismus.[1] Today, most investigators agree that hyperopia appears to have an important influence on the development of accommodative esotropia.[2] We studied two sets of monozygotic twins and the findings strongly support the notion that the degree of hyperopia and anisometropia influences the ocular alignment of individuals predisposed to developing accommodative esotropia.

One member of each of two sets of monozygotic female twins reared together had accommodative esotropia. No child weighed less than 1,800 g at birth or had a gestational age of less than 36 weeks. There were no complications at delivery in either pair. In each case, the member who developed esotropia was delivered first and weighed the most. Placental pathologic studies showed diamniotic, monochorionic twin placentas in both cases. Both sets of twins fulfilled the Nichols and Bildro criteria for monozygosity, which has been independently determined to be 90% reliable.[3] No evidence of lateral rectus muscle palsy or strabismus syndrome was observed in any child.

The first set of twins was examined at age 2 years 5 months, 45 days after the first episode of esotropia in twin A (Figure). Twin A manifested a constant 30-diopter comitant left esotropia at both distance and near fixation. Twin B was orthophoric. Cycloplegic refraction in twin A was $+3.00 +0.50 \times 90$ in the right eye and +4.00 sphere in the left eye. Twin B was +2.00 sphere in the right eye and +2.50 sphere in the left eye. The second pair of twins was first examined at age 3 years 5 months, two days after the onset of esotropia in twin A. Twin A manifested a constant 40-diopter right esotropia at both distant and near fixation. Twin B was orthophoric. Cycloplegic refraction in twin A was +4.50 sphere in the right eye and +3.50 sphere in the left eye. Twin B was +4.00 sphere in the right eye and +3.00 in the left eye. With full cycloplegic correction, orthophoria was restored in both esotropic children. Spectacle correction was not given to either orthophoric child and, after 12 months of follow-up, neither has developed an esotropia.

Previous twin studies have supported both dominant and recessive inheritance in comitant strabismus.[1,4,5] Today, the most widely accepted mode of transmission is multifactorial with a threshold effect. In monozygotic twins reared together one might expect simultaneous onset

Figure (Bucci, Catalano, and Simon). Left, Photographic record of twin set 1 demonstrating esotropia in one member. Right, Orthophoria restored in esotropic twin with spectacle correction.

of strabismus. The only unequal variable in each of our twin pairs, to our knowledge, was the degree of hyperopia. The finding that the more hyperopic eye in the more hyperopic twin pair manifested the strabismus is apparent evidence that hyperopia is a substantive factor contributing to the multifactorial mode of inheritance. It could be easily argued that the greater hyperopia in the strabismic twins advanced these predisposed children beyond the threshold required to express this particular defect.

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Sudden Unilateral Visual Loss After Autologous Fat Injection Into the Glabellar Area

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Plastic surgeons, dermatologists, and others have developed techniques using injectable substances, such as autologous fat, to correct a variety of body defects. We recently observed an unusual case of visual loss after the facial injection of autologous fat.

A 44-year-old woman underwent autologous fat injection into the forehead to remove facial wrinkles. The procedure was performed by a plastic surgeon at another institution. Several milliliters of abdominal fat were removed with a needle attached to a syringe and immediately injected into the glabellar area. The patient returned to the surgeon nine days later, and because of remaining wrinkles, the process was repeated. The patient immediately complained of severe right hemicranial pain and total loss of vision in the right eye.

The patient was seen at our institution four days after her visual loss. Best-corrected Snellen visual acuity was R.E.: no light perception and L.E.: 20/25. The right upper eyelid was mildly blepharoptotic, and the right globe showed 2 mm of proptosis. The right pupil was nonreactive to direct light and a relative afferent pupillary defect was present. Biomicroscopy showed mild diffuse injection of the right conjunctiva and a small inferonasal subconjunctival hemorrhage on the right. Intraocular pressure by applanation tonometry was normal in both eyes. Ophthalmoscopy of the right eye demonstrated a pale, swollen optic disk. Many branches of the right retinal arterioles were segmentally occluded with opaque yellow material (Fig. 1), and the posterior pole was pale yellow. No cherry-red spot was present. The left fundus was normal. A fluorescein angiogram showed no filling of the retinal arterioles of the right eye and only minimal splotchy filling of the right choroid. There was no measurable response to a flash electroretinogram in the right eye.

On examination 2½ months later, visual acuity remained no light perception in the right eye and the mild proptosis and conjunctival injection had completely resolved. The optic nerve remained pale, the retinal arterioles still contained some emboli, and the posterior pole demonstrated a few scattered retinal hemorrhages and mottling of the retinal pigment epithelium. The peripheral fundus of the right eye also demonstrated segmental retinal pigment epithelial mottling in wedge-like configurations (Fig. 2).

The findings in this case are consistent with multiple fat embolic occlusions of distal branches of the ophthalmic artery. Emboli within the retinal arterioles were directly observed. The pale, swollen optic disk initially seen indicates that emboli were occluding vessels supplying the optic nerve. The proptosis,

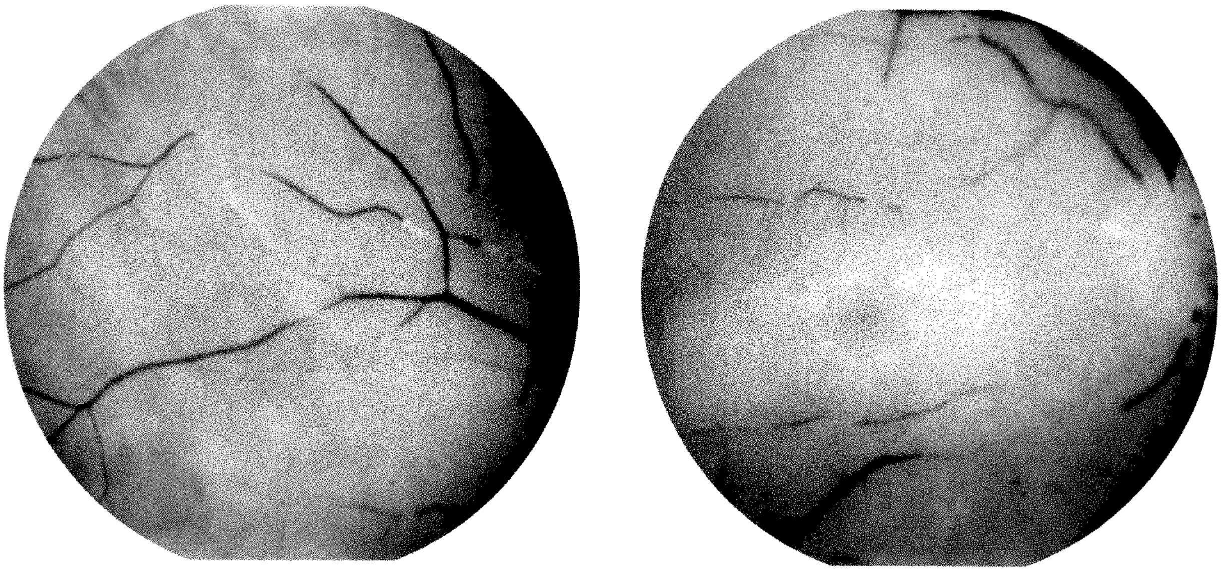

Fig. 1 (Dreizen and Framm). Fat emboli occluding superotemporal (left) and macular (right) retinal arterioles.

blepharoptosis, and conjunctival injection suggest that distal branches of the ophthalmic artery supplying the orbit became occluded, leading to orbital inflammation. Finally, the absence of a cherry-red spot, the patchy choroidal filling as demonstrated by fluorescein angiography, the flat electroretinogram, and the ultimate wedge-like retinal pigment epithelial disturbances all provide evidence that flow to the choroid via the short posterior ciliary arteries was compromised.

Fig. 2 (Dreizen and Framm). Peripheral wedge-shaped area of retinal pigment epithelial mottling.

We postulate that the autologous fat was inadvertently injected into a distal forehead branch of the ophthalmic artery, such as the supratrochlear artery. Under pressure exerted by the syringe, the fat traveled retrograde at least to the main trunk of the ophthalmic artery. Once the pressure from the syringe ceased, the fat reversed direction and was propelled anterograde by the patient's blood pressure, breaking up and occluding the small distal branches of the ophthalmic artery.

Sudden visual loss after periocular, nasal, and other facial injections of corticosteroids, anesthetic agents, and collagen has been well documented.[1-5] Vascular occlusion or spasm of the retinal or choroidal vasculature was thought to be the cause of visual loss in all of these cases. As in our case, the foreign material was postulated to have been injected into a distal branch of the ophthalmic artery, through which the retinal and choroidal circulation could be reached. Surgeons who administer injections of autologous fat into areas supplied by distal branches of the ophthalmic artery should be aware of the potential complication of visual loss.

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Staphylococcus aureus Conjunctivitis and Sepsis in a Neutropenic Patient

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In November 1987, metastatic small cell carcinoma of the lung was diagnosed in a 70-year-old man. Treatment included cisplatin, doxorubicin, cyclophosphamide, etoposide, and gamma-interferon. His first course was complicated by *Streptococcus pneumoniae* sepsis cultured from a symptomatic throat infection while he was neutropenic.

He was readmitted ten days after completion of his second course of chemotherapy with neutropenia (white blood cell count of 300) and a three-day history of redness, moderate drainage, and mild discomfort in the left eye. The patient was unaware of any visual disturbances. He became febrile (103 F) and had tachypnea and rigors the day before admission. On physical examination, there were no symptoms or signs of a focal infection elswhere.

Previously, the patient was last seen and treated in our eye clinic for bilateral aphakia and recurrent retinal detachments in 1981. His visual acuity at that time was R.E.: hand motions and L.E.: 20/100. During his current admission he denied seeing light in the right eye; visual acuity in the left eye remained 20/100. His symptomatic left eye had mild conjunctival injection, scant drainage, and no signs of intraocular inflammation. No intraocular inflamma-

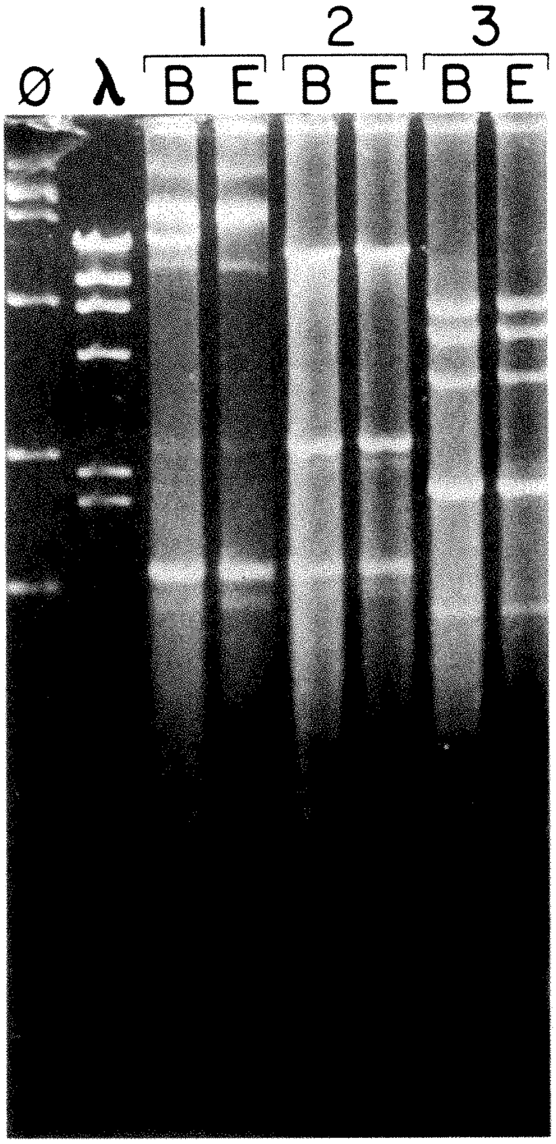

Figure (Wolf and associates). Agarose gel electrophoresis of digested and undigested plasmid DNA from blood (B) and conjunctival (E) isolates of *Staphylococcus aureus*. Lane 1 (ϕ), reference undigested plasmid DNA (New England Nuclear, Boston, Mass) and Lane 2 (λ), reference lambda phage DNA (Hind III Digested) are standard molecular weight markers; Lanes 3 and 4 (Group 1), undigested plasmid DNA from blood and conjunctival isolates; Lanes 5 and 6 (Group 2), plasmid DNA digested with Eco R1; Lanes 7 and 8 (Group 3), plasmid DNA digested with Hind III. In each case the patterns observed with the blood and conjunctival isolates were identical.

tion was seen in association with the scleral buckles. Intraocular pressure was R.E.: 36 mm Hg and L.E.: 14 mm Hg. Indirect ophthalmoscopy with a dilated pupil did not show any acute inflammatory or infectious changes within the eye.

Cultures of the left conjunctiva and blood both grew *Staphylococcus aureus*, whereas urine, throat, sputum, and stool cultures produced no growth. The conjunctival and blood isolates were identical with respect to biochemical profile and antibiotic susceptibility pattern.

Further proof that the two isolates were identical was obtained by restriction endonuclease analysis of plasmid DNA (Figure).[1] These findings indicated that the two isolates originated from a single clone. Since ocular infection preceded the onset of systemic complaints, it is probable that the ocular infection was the source of the patient's bacteremia.

Based on results of the cultures and sensitivities, a six-week course of systemic nafcillin and topical tobramycin was started. The systemic signs of sepsis and the ocular signs and symptoms responded, as did his white blood cell count during the first three days of therapy. The patient was discharged after six weeks and has subsequently received three further courses of chemotherapy.

In the present case, the sequence of clinical events coupled with the finding that the conjunctival and blood culture isolates of *S. aureus* were identical by plasmid DNA restriction fragment analysis provides convincing evidence that the bloodstream infection was secondary to staphylococcal conjunctivitis. Although *Pseudomonas aeruginosa* vasculitis and bacteremia have been produced in neutropenic rabbits via conjunctival sac instillation of organisms, bacteremia could not be produced by *Escherichia coli, Klebsiella* pneumonia, or non-*aeruginosa Pseudomonas*.[2] Burns and Rhodes[3] documented fatal *Pseudomonas* sepsis in premature infants following conjunctivitis; however, similar sequelae have not been conclusively documented in adults. It is possible that neutropenia may limit conjunctival signs of inflammation. It is also possible that in a severely systemically ill patient a mild conjunctivitis may not be detected.

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Iridoschisis Associated With Syphilitic Interstitial Keratitis

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Iridoschisis, which most commonly occurs in the elderly, has a sectoral distribution with an unexplained predilection for the inferior portion of the iris. Case reports and series have described associated ocular conditions that can be grouped into the broad categories of trauma, congenital anomalies, and conditions associat-

Fig. 1 (Pearson and associates). Profile of patient demonstrating saddle nose deformity.

ed with aging.[1] We encountered a case in which iridoschisis was associated with interstitial keratitis secondary to congenital syphilis.

An 89-year-old woman was examined for complaints of a gradual decrease in vision over the previous several months. Her medical history was remarkable for a bilateral sensorineural hearing loss requiring the use of hearing aids since the age of 25 years, extraction of all teeth at age 25 years because of Hutchinson's teeth, and a saddle nose deformity secondary to syphilitic rhinitis (Fig. 1).

Visual acuity was R.E.: 20/400 and L.E.: 20/200. Dense nuclear sclerotic cataracts were believed to be the principal cause of her decreased vision. Intraocular pressure was R.E.: 8 mm Hg and L.E.: 5 mm Hg. The pupils were 3.5 mm bilaterally and slightly irregular in shape; there was no relative afferent defect. Slit-lamp examination demonstrated ghost vessels and corneal opacities characteristic of interstitial keratitis in both eyes. There was iridoschisis bilaterally in the inferior quadrants of each iris and a portion of the iris stroma was in contact with the corneal endothelium in the left eye (Fig. 2). Atrophy of the retinal pigment epithelium was evident on ophthalmoscopy in both eyes. Gonioscopy showed the angles to be open to the scleral spur for at least seven clock hours superiorly. The inferior angles were difficult to assess.

Iridoschisis was first reported in 1922 by Schmitt[2] who described a case of "separation of the anterior layer of the iris." Lowenstein, Forster, and Sledge[3] applied the term iridoschisis to describe this focal cleavage of the mesodermal iris stroma at the anterior and posterior layer interface. In this condition, the anterior iris layer separates from the deeper muscular layer and bulges forward into the anterior chamber. The strands of the anterior layer eventually break, the ends remaining attached to the root of the iris or to the iris sphincter, and the loose ends float freely in the anterior chamber. There is no iris hole formation. The pupil has normal centering and reacts normally. Many processes common in the elderly have been described in association with iridoschisis including arcus cornealis, iridocyclitis, and cataracts. Glaucoma occurs in about 50% of cases. Corneal changes are also common. These include corneal edema, endothelial dysfunction, endothelial rarefaction, and focal endothelial defects overlying the area of iridoschisis.[1]

In a previous report of iridoschisis associated with congenital syphilis,[4] the cornea was de-

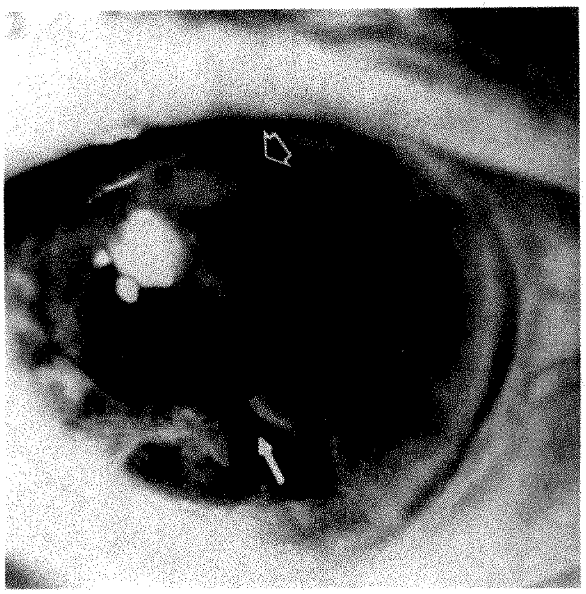

Fig. 2 (Pearson and associates). Photograph demonstrating interstitial keratitis superiorly (open arrow) and iridoschisis inferiorly (closed arrow).

scribed as clear and there was no evidence of interstitial keratitis. In a second report,[5] the history and results of examination were consistent with syphilitic interstitial keratitis. Our patient has the stigmata of congenital syphilis, including Hutchinson's teeth, sensorineural hearing loss, a saddle nose deformity, and interstitial keratitis.

Iridoschisis is a rare condition, with approximately 100 reports in the literature. Because syphilitic interstitial keratitis is also relatively uncommon, we believe that the occurrence of iridoschisis with congenital syphilis may be more than random association. The presence of iridoschisis should not only alert the physician to the likelihood of glaucoma, but should also warrant investigation for possible congenital syphilis.

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Ocular Myasthenia Gravis Associated With Autoimmune Hemolytic Anemia and Hashimoto's Thyroiditis

Yasuo Iwasaki, M.D., and Masao Kinoshita, M.D.

Fourth Department of Internal Medicine, Toho University Ohashi Hospital.

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We studied a patient with ocular myasthenia gravis, autoimmune hemolytic anemia, and Hashimoto's thyroiditis. This case suggests that these disorders may be related.

A 62-year-old Japanese woman was referred to our clinic with a one-month history of bilateral blepharoptosis. She had a history of autoimmune hemolytic anemia, and had been treated with 5 mg of prednisolone per day for three years. On examination, mild anemia and bilateral minimal diffuse thyroid enlargement with a hard surface were noted. Results of neurologic examination were normal. Marked bilateral blepharoptosis without ophthalmoplegia was present. The pupils were isocoric and reactive. Results of motor examination of all extremities were normal. A single dose of 2 mg of edrophonium chloride administered intravenously immediately reversed the blepharoptosis. Results of laboratory examinations included normal electrolyte levels and liver function tests, and the total bilirubin level was 2.0 mg/dl (indirect bilirubin was 1.9 mg/dl). Results of complete blood cell counts were as follows: white blood cell count, 3,100/mm^3; red blood cell count, 3.26 $\times$ 10^6/mm^3; hemoglobin, 10.1 g/dl; and platelet count, 1.19 $\times$ 10^4/mm^3. The antibody tests demonstrated a microsomal antibody of 1:1,600 and a thyroglobulin antibody of 1:1,600. The thyroid stimulating hormone level was 32 μM/ml (normal, <10 μM/ml). The T_4, T_3, and free T_4 values were 7.4 μg/dl (normal, 5.0 to 13.0 μg/dl), 100 ng/l (normal, 70 to 190 mg/l), and 0.7 ng/dl (normal, 1.1 to 2.0 ng/dl), respectively. Results of both the direct and indirect Coomb's tests were positive. The measurement of anti-acetylcholine receptor antibody titer in the blood was 0.02 pmol/ml (normal, <0.5 pmol/ml). On electromyography, typical waning waves were noted in the orbicularis oculi. Results of computed tomography of the brain were normal. No detectable thymoma was observed in the overall body computed tomographic scan.

A diagnosis of ocular myasthenia gravis was made on the basis of the ocular signs, positive edrophonium chloride test, and electromyographic findings, although the anti-acetylcholine receptor titer was not increased. Diagnosis of autoimmune hemolytic anemia was based on mild anemia, increased level of indirect bilirubin, and positive direct and indirect Coomb's tests. Physical examination showed minimal diffuse thyroid enlargement with a hard surface. Laboratory studies showed normal values of T_3 and T_4, an increased level of thyroid stimulating hormone, and decreased free T_4. Positive thyroglobulin and microsomal thyroid antibodies were present. These findings were compatible with a diagnosis of Hashimoto's thyroiditis, although no biopsy of the thyroid gland was performed.

It is well known that myasthenia gravis is found in association with other autoimmune diseases, and four cases of myasthenia gravis associated with autoimmune hemolytic anemia have been reported.[1-4] A combined occurrence of myasthenia gravis and Hashimoto's thyroidits is rare.[5] Moreover, myasthenia gravis, autoimmune hemolytic anemia, and Hashimoto's thyroiditis occurring together is an unusual constellation of autoimmune disorders. Since myasthenia gravis is associated with many autoimmune diseases, we suggest that full antibody testing be performed on a patient with this disease.

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Correspondence

Correspondence concerning recent articles or other material published in The Journal should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

Nasolacrimal Drainage System Obstruction After Orbital Decompression

EDITOR:

In the article "Nasolacrimal drainage system obstruction after orbital decompression" by Stuart R. Seiff and Norman Shorr (Am. J. Ophthalmol. 106:204, August 1988), the authors identified a significant complication of orbital decompression surgery, namely, nasolacrimal duct obstruction and epiphora. In their series, all of their patients who developed this complication underwent transantral decompressions with nasoantral windows. They speculated that the obstructions may have been the result of progressive cicatricial scarring of the distal nasolacrimal duct.

I perform orbital decompression surgery through a transconjunctival approach, routinely creating a nasoantral window and placing a Foley catheter in the sinus for drainage. After removing the orbital floor and medial wall, but before making the nasoantral window, I insert a No. 00 Bowman probe from the upper punctum through the nasolacrimal duct. I can then inspect the lacrimal sac for inadvertent tears and detect any irregularities in the nasolacrimal duct with the probe. Lastly, I create the nasoantral window with a hemostat, leaving the probe in place so that the nasolacrimal duct and Hasner's valve can be avoided.

I have probed the lacrimal drainage system on the last seven orbital decompressions that I have performed. One patient had a small tear in the lacrimal sac that was repaired with a single interrupted 6-0 Vicryl suture and silicone intubation. There has been no epiphora in this patient in 12 months of follow-up. In none of the other six cases was nasolacrimal duct obstruction noted at the time of surgery, and none of these patients have complained of epiphora during the follow-up period of four to 18 months.

This simple additional step should be performed with each orbital decompression, regardless of the approach, to identify treatable damage to the lacrimal drainage system immediately.

MICHAEL E. MIGLIORI, M.D.
Providence, Rhode Island

Reply

EDITOR:

We applaud Dr. Migliori's efforts to avoid nasolacrimal drainage system obstruction after orbital decompression. We believe a surgeon should take whatever steps are considered necessary to preserve the integrity of the lacrimal drainage system in such procedures. Dr. Migliori's experience of a lacerated lacrimal sac is further evidence of the high incidence of this problem. We were interested to note that the lesion was high in the system (sac) and occurred during a transconjunctival decompression. This is not where we anticipated lesions via the transantral approach, as it is anteriorly removed from the surgical site.

Placing a probe in the lacrimal outflow system may allow early identification of a violation of its integrity and permit its repair. However, we would optimally like to avoid such an acute disruption of the system and lesions which might lead to late cicatricial obstruction, as well. We believe this can best be accomplished through meticulous surgical decompression and identification of anatomic structures in the operative field. This approach seems to have been helpful in pre-

venting lacrimal drainage system injuries during the past two years, but it is still too early to tell.

STUART R. SEIFF, M.D.
San Francisco, California
NORMAN SHORR, M.D.
Los Angeles, California

EDITOR:

In the article "Nasolacrimal drainage system obstruction after orbital decompression" by Stewart R. Seiff and Norman Shorr (Am. J. Ophthalmol. 106:204, August 1988), an impressive series of 123 cases of orbital decompression were reviewed. In 90 cases of transantral ethmoidal orbital decompression, 14 (16%) resulted in epiphora. A high percentage of these patients were cured with the use of a dacryocystorhinostomy.

I have been performing orbital decompression surgery for thyroid orbitopathy for many years using the infra-eyelid approach and have not found it necessary to do this operation in conjunction with a Caldwell-Luc procedure. Most of the decompressions are medial and floor decompressions. It has been my experience that this approach to the posterior orbital apex has been an excellent one with good visualization. Only in one case during the procedure was the nasal lacrimal duct itself penetrated; however, it was repaired at the time and there was mild epiphora. In all of my cases there was no nasal lacrimal duct obstruction after medial and inferior orbital decompression using the infra-eyelid approach.

I therefore congratulate the authors for bringing to our attention the complication of nasal lacrimal drainage obstruction after orbital decompression, but suggest strongly that the infra-eyelid approach or inferior cul-de-sac should be recommended, since I believe it affords the best visualization with the fewest complications.

ALBERT HORNBLASS, M.D.
New York, New York

Reply

EDITOR:

We thank Dr. Hornblass for his comments. Our study certainly supports the premise that such obstruction is more common via the transantral approach than the transconjunctival route. However, this should not be interpreted to mean that the transantral approach is any less appropriate or useful. In our study, we suggested that the obstructing lesion is most likely related to placement of the nasoantral window, rather than the decompression itself. Careful avoidance of the nasolacrimal drainage system while creating the window, or eliminating the window entirely, is likely to minimize this problem in the future. We firmly believe that the transantral approach is preferred for cases of significant compressive optic neuropathy as it offers better visualization of the orbital apex than does a transeyelid approach. Additionally, the transantral approach is technically simpler in our hands in cases of severe proptosis.

Dr. Hornblass states that he has recognized damage to the lacrimal drainage system during a transeyelid procedure. This points out that the lacrimal drainage system is in jeopardy during any type of orbital decompression and that such lesions are not uncommon. Different surgeons may find a given technique more suitable for them in a particular case. However, whatever approach is chosen, great care must be taken to avoid the nasolacrimal drainage system during orbital decompression and in placing any associated nasoantral window.

STUART R. SEIFF, M.D.
San Francisco, California
NORMAN SHORR, M.D.
Los Angeles, California

The Effect of Suture Removal on Postkeratoplasty Astigmatism

EDITOR:

I enjoyed the article "The effects of suture removal on postkeratoplasty astigmatism" by Perry S. Binder (Am. J. Ophthalmol. 105:637, June 1988). I, too, practice the technique of removing the sutures one at a time in the meridian of steepest astigmatism, which can have a gratifying effect on visual acuity in the postoperative period. Many times, the reduction allows fitting with a contact lens while some sutures are still in place.

The question is, does the selective removal of the sutures affect the eventual outcome of the amount of astigmatism after all sutures have been removed or have biodegraded? I do not think that Dr. Binder's study has answered this question. In order to do so, he would have to compare a group of eyes undergoing selective suture removal to a group

of similar eyes undergoing removal of all sutures at one time.

Dr. Binder reports an average residual astigmatism of 3.5 diopters (range, 0 to 10.00 diopters), and he cites the results of other authors who report postoperative astigmatism of 3.5 to 5.2 diopters. I have just reported on 72 eyes that underwent penetrating keratoplasty for keratoconus.[1] The mean postoperative astigmatism was 3.66 diopters (range, 0.50 to 10.00 diopters) when all sutures were removed between three and four months postoperatively.

I believe that selective suture removal after penetrating keratoplasty can give more rapid visual rehabilitation of the patient, but I question whether it affects the final outcome of the postoperative astigmatism after all sutures have been removed.

I am happy to see that Dr. Binder is reporting his results after all sutures have been removed and with significant postoperative follow-up, a procedure which I have advocated for a number of years. Evaluation of the astigmatism while the sutures are still in place is worthless.

LOUIS J. GIRARD, M.D.
Houston, Texas

Reference

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Reply

EDITOR:

Dr. Girard is correct that my study did not answer the question "Does the selective removal of sutures affect the eventual outcome of the amount of astigmatism after all sutures are removed?" In order to answer that question, I would have to perform a prospective, randomized study of patients with single or double continuous sutures compared with patients randomly receiving the selective suture removal technique.

My previous studies[1-5] demonstrated that the selective suture removal could reduce postkeratoplasty astigmatism while the continuous 16-μm suture and other interrupted 10-0 monofilament nylon sutures were in place. The currect study demonstrated that once all sutures are removed, the final astigmatism can be acceptable. In this particular study, the mean astigmatism for 188 eyes was considerably lower than that reported by other authors. Although Dr. Girard reports a similar amount of astigmatism for 72 eyes with keratoconus, I also mentioned that an analysis of one individual group, such as patients with keratoconus, could spuriously suggest better results. Indeed, the 66 eyes with keratoconus in my study had a mean astigmatism much lower than the entire group mean.

As stated in my article, one of the theories behind the selective removal of sutures is that once a configuration is achieved, the cornea is allowed to remain in that configuration while wound healing takes place; once sutures are removed, that same amount of astigmatism will be maintained. I was unable to prove this point in the current series of patients because some eyes had a reduction in astigmatism after suture removal, whereas others had an increase or no change. Ideally, there should be no change in the astigmatism after suture removal.

Dr. Girard and I both agree that it would be desirable to eliminate postkeratoplasty astigmatism. Suture removal techniques can only partially modify the errors we create through trephination and by abnormalities in wound healing that occur postoperatively.

PERRY S. BINDER, M.D.
La Jolla, California

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BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Ophthalmic Photography. By J. Michael Coppinger, Mark Maio, and Kirby Miller. Thorofare, New Jersey, Slack Inc., 1988. Softcover, 134 pages, index, illustrated. $35

Reviewed by CSABA L. MARTONYI
Ann Arbor, Michigan

Written as one of 12 in a series on ophthalmic technical skills, this is also a complete, standalone text on ophthalmic photography. It begins beautifully with an introduction to the basic principles of light as the fundamental element of photography. A refreshing amount of technical information is presented in a matrix of readable, user-friendly text. This is followed by a thorough description of the basic 35-mm camera and its use. Other fundamentals of photography are also covered and provide an all-important foundation for the subjects that follow.

Patient photography is addressed in all major applications. Modalities covered include external and slit-lamp photography, endothelial specular micrography, fundus photography (including stereoscopic), and fluorescein angiography. A chapter is devoted to each, and all are discussed in good detail and well supported with illustrations. Black and white film processing is also presented in a brief chapter.

The contraindications to fluorescein angiography and the medical intervention for reactions to intravenous fluorescein are somewhat aggressively detailed in a text written specifically for technicians. The wording used might, inadvertently, suggest that a technician assume a greater level of responsibility than may be appropriate.

Many errors, both typographical and technical, were found. Without correction, some may prove confusing for the novice. However, some corrections have already been made and reprinted pages are available from the publisher or the first author. Further corrections are planned. The binding of this book facilitates replacement of pages.

This work is not referenced. The authors have elected, instead, to provide a short reading list of publications on related subjects under "Additional Sources of Information."

Overall, this book is a good source of information for those interested in learning ophthalmic photography. A strength of this textbook is its listing of the steps necessary to carry out most ophthalmic photographic procedures. Much of the text is presented in a buoyant, somewhat informal style, reflecting the authors' enthusiasm for the subject.

Textbook of Ophthalmic Plastic and Reconstructive Surgery. By Roger Kohn. Philadelphia, Lea & Febiger, 1988. 344 pages, index, illustrated. $95

Reviewed by ROBERT C. KERSTEN
Cincinnati, Ohio

This book is intended as a comprehensive guide to ophthalmic plastic, reconstructive, and orbital surgery. It begins with general chapters on anatomy, physiology, and basic surgical principles, followed by specific chapters dealing with the diagnosis and management of congenital and acquired ophthalmic plastic abnormalities. These include congenital anomalies of the eyelid and socket, craniofacial abnormalities, blepharoptosis, thyroid ophthalmopathy, ectropion, entropion, blepharoplasty, eyelid reconstruction, conjunctival surgery, the anophthalmic socket, the lacrimal system, essential blepharospasm, orbital tumors, and orbital fractures. Dr. Kohn, an experienced ophthalmic plastic surgeon, is the author of all of the chapters except those concerning craniofacial abnormalities (Andrew Choy) and orbital tumors (James Orcutt).

Each chapter is organized to present the pathophysiology, differential diagnosis, evaluation, and management of the various disorders. The book is written in an easy-to-read style and the accompanying illustrations are handsomely drawn. The techniques described are those currently used by Dr. Kohn. Generally, he has succeeded in the difficult task of providing succinct, detailed descriptions of the steps in the various surgical procedures. How-

ever, the book relies exclusively on drawings to demonstrate surgical procedures rather than on intraoperative photographs. At times, the illustrations seem to present imprecisely the surgical anatomy, and the reader may find it difficult to duplicate the described surgical procedures for this reason.

The book is billed as the updated sequel to the 1976 edition of "Practical Ophthalmic Plastic and Reconstructive Surgery" by Drs. Reeh, Beyer, and Shannon. The ideas presented in this edition generally reflect the progress that has been made in this field over the past decade. However, there are a number of areas in which more recent material has not been included. For example, many now question the concept of separate reflex and basic tear secretions, or Jones and Wobigs' theory of lacrimal pump function, both of which have been seemingly contradicted by recent evidence. Most plastic surgeons trained in the past decade would not agree with Dr. Kohn's assessment of silk as the "ideal skin suture," and would certainly be surprised at Drs. Kohn and Orcutt's statement that an incision placed directly over the infraorbital rim provides "an excellent approach for repair of blowout fractures."

The text reflects a tremendous effort, which has resulted in complete coverage of the field of ophthalmic plastic and reconstructive surgery. It nicely presents one man's view of this field, and will be of interest to many ophthalmologists.

Lacrimal Surgery. Contemporary Issues in Ophthalmology, vol. 5. Edited by John V. Linberg. New York, Churchill Livingstone Inc., 1988. 348 pages, index, illustrated. $79

Reviewed by JOHN L. WOBIG
Portland, Oregon

Twenty-four authors have organized an excellent book on the diagnosis and treatment of lacrimal disorders. Nine chapters deal with surgical procedures for the repair of the lacrimal system. The remaining chapters deal with anatomy, pathology, and radiography of the lacrimal system. The chapter on diagnostic tests and imaging techniques, by Jonathan Dutton, is an excellent summary of all available diagnostic tests: ultrasonography, radionuclide dacryoscintigraphy, computed tomography, and chemiluminescence are nicely summarized for the clinician.

The chapter on the pathology of nasolacrimal duct obstructions, by Steven A. McCormick and John V. Linberg, is original and worthwhile. The chapter on the surgical management of lacrimal sac tumors, by Joseph C. Flanagan and Christine Zolli, is valuable. It is a subject that has been neglected in other lacrimal books. This well-organized book is enhanced by Dr. Linberg's comments on controversies in the lacrimal field. This book will be of value to residents in ophthalmology and to practicing ophthalmologists with an interest in lacrimal surgery.

Amaurosis Fugax. Edited by Eugene F. Bernstein. New York, Springer-Verlag New York, Inc., 1988. 310 pages, index, illustrated. $75

Reviewed by JONATHAN D. TROBE
Ann Arbor, Michigan

This book is a collection of 21 essays contributed by a group of experts who assembled at the Scripps Clinic and Research Foundation in La Jolla, California, in March 1987. The editor, Eugene F. Bernstein, a vascular surgeon at Scripps, organized this gathering of prominent representatives from the clinical neurosciences, ophthalmology, hematology, and vascular surgery under one roof and, now, under one book cover.

The result earns a mixed review. Nowhere else can one find an authoritative essay on the vascular anatomy of the eye (Hayreh) together with a solid discussion of antithrombotic agents (Harker) and recent reviews of endarterectomy for amaurosis by neurosurgeons (Fode and Sundt) and vascular surgeons (Connelly, Okuhn, and Ehrenfeld) in a single source. The bibliography alone is worth the price of the book. Another laudable feature is the "Consensus Statement" at the end of the book. It is an eloquent synopsis of "where we are today" in the diagnosis and treatment of amaurosis fugax.

There are, however, several criticisms to be

made. The essays are, for the most part, thin on insight and scholarship. For example, no one thoroughly examines the historic development of the thromboembolic theory of amaurosis fugax. No one addresses the classic epidemiologic quandary of whether cervical carotid atheroma causes amaurosis fugax or is merely associated with it. Gautier writes "lesions of the ICA [internal carotid artery] by far rank first as a cause of amaurosis fugax." Harrison notes that the "very high prevalence of atheromatous disease in the ipsilateral ICA is evidence in favour of the belief that small friable emboli that cause fleeting visual loss commonly originate at the carotid bifurcation." Yet, in an earlier chapter, Otis reports that noninvasive carotid studies show an identical prevalence of stenosis in patients with unilateral and bilateral amaurosis fugax. It is uncertain whether the carotid disease also caused the bilateral visual loss.

Most of the authors simply pass along traditional ideas without discussing their shaky underpinnings. For instance, Wray writes that "data suggest a different pathogenic mechanism" for central and branch retinal artery occlusion, citing a 1979 study that showed, without statistical analysis, that a higher proportion of patients with central artery occlusion had documented hypertension. It is never clear what pathogenic mechanisms Wray invokes. In describing the natural course of patients with amaurosis fugax or cholesterol retinal emboli, Russell reports that stroke is much more common in these patients than in age-matched controls. That may be true, but he omits the important follow-up point that many of these strokes may not be in the domain of the carotid artery, or may be lacunar infarcts rather than artery-to-artery embolic infarcts. The "Consensus Statement" bases a recommendation for endarterectomy in patients with greater than 75% cervical carotid stenosis on the assumption that "high degrees of stenosis are associated with an increased risk of stroke." There is a vast and conflicting literature on this critical point, none of which is cited in the book.

The most disheartening aspect of this book is the realization that little meaningful information about amaurosis fugax has been gathered in the past 15 years. The clinical descriptions were admirably reported many years ago. Most of the epidemiologic studies are flawed and must now be redone with more attention to rigorous epidemiologic methods and imaging. Sadly, none of the pathophysiologic questions posed by the editor in the foreword were answerable. The book would have been much stronger had it contained a solid contribution by an epidemiologist discussing the loopholes in our knowledge and how we might go about closing them. Such a chapter might at least have acknowledged the three ongoing controlled clinical trials of carotid endarterectomy that were about to start when this book went to press. That omission reminds us that there is still little consensus in the management of amaurosis fugax and other forms of threatened stroke.

Books Received

1988 Year Book of Ophthalmology. Edited by J. Terry Ernest and Thomas E. Deutsch. Chicago, Year Book Medical Publishers, Inc., 1988. 268 pages, index, illustrated. $44.95

Although harcovered, this book is ephemeral and should be read before next year's edition appears. The editors have scanned the recent literature and have generated short abstracts of the papers they find interesting. Appeal will be to those who think they are not keeping up, which is almost all of us. Wherever the book is opened, an interesting morsel can be quickly picked up, and for the reader who cannot get through a half page abstract before the phone rings, Dr. Deutsch has provided a two-sentence capsule after each article.

Boletin del Instituto Nacional de Investigaciones Oftalmologicas, vol. 6, 1988. Caracas, Instituto Nacional de Investigaciones Oftalmologicas. 324 pages, softcover, illustrated.

Twenty-five papers from Professor Eduardo Grom's department on a wide variety of subjects.

Treinta Anos del Servicio de Oftalmologia. Hospital Universitario de Caracas 1958–1988. Caracas, Instituto Nacional de Investigaciones Oftalmologicas, 1988. 268 pages, softcover, illustrated.

A history of the Ophthalmology Service of the University of Caracas, Venezuela.

ABSTRACT DEPARTMENT

Edited by David Shoch, M.D.

Acta Ophthalmologica

A comparison of betaxolol and timolol in open angle glaucoma and ocular hypertension. Feghali, J. G., Kaufman, P. L., Radius, R. L., and Mandell, A. I. (Dept. Ophthalmol., West Virginia Univ. School of Med., Morgantown, WV 26506). Acta Ophthalmol. 66:180, 1988.

Forty-one patients with primary open-angle glaucoma or ocular hypertension were treated in a randomized, double-masked fashion for 26 weeks with either 0.5% betaxolol or 0.5% timolol. Both drugs were effective in reducing intraocular pressure. The average decrease with betaxolol was 6.3 mm Hg and with timolol, 7.2 mm Hg. There was a small decrease in the brachial arterial pressure with timolol, but this was not statistically significant. Pulse, pupil size, and tear secretion were unchanged. There were more complaints of burning with the betaxolol than with timolol. (3 figures, 1 table, 30 references)—David Shoch

Pseudopapilledema associated with abnormally small optic discs. Jonas, J. B., Gusek, G., Guggenmoos-Holzmann, I., and Naumann, G. (Dept. Ophthalmol. and Eye Hosp. of the University Erlangen-Nurnberg, Schwabachanlage 6, D-8520 Erlangen, West Germany). Acta Ophthalmol. 66:190, 1988.

The authors photographed the optic nerve heads of 35 patients with pseudopapilledema. The average optic disk area was 1.95 ± 0.33 mm^2 as compared to 2.73 ± 0.76 mm^2 for normal optic nerve heads. The difference was significant ($P < .001$). The disks with pseudopapilledema did not show any cupping. The authors suggested that this markedly reduced size of the optic nerve head associated with a small optic nerve scleral canal may interfere with the axoplasmic flow, resulting in some secondary swelling of the optic nerve fibers. This study also indicates that both hyperopia and myopia occur with pseudopapilledema. The mean refraction of the patients was $+1.2 \pm 1.4$ diopters, which is about the same as the mean refraction found in large populations. (1 figure, 2 tables, 19 references)—David Shoch

American Journal of Pediatric Hematology/Oncology

Xanthoma disseminatum. An unusual histiocytosis syndrome. Giller, R. H., Folberg, R., Keech, R. V., Piette, W. W., and Sato, Y. (Dept. Pediatr., Univ. Iowa Hosp. and Clinics, Iowa City, IA 52242). Am. J. Pediatr. Hematol. Oncol. 10:252, 1988.

The histiocytoses are a group of diseases whose origin is unknown. All are characterized by proliferation of mononuclear phagocytes. These diseases have been grouped clinically by the organ involved. It has now been suggested that the histiocytic syndromes be subdivided according to the pathologic features of the cells involved rather than the clinical findings. The first group, formerly called histiocytosis X, includes diseases in which proliferations of Langerhans' cells are present. These include eosinophilic granuloma, Hand-Schuller-Christian syndrome, and Letterer-Siwe disease. The second category includes such diseases as hemophagocytic lymphohistiocytosis and juvenile xanthogranuloma. The third group includes the malignant neoplastic disorders such as acute monocytic leukemia and true histiocytic lymphoma. The patient described was an 8-year-old boy with xanthoma disseminatum, which falls into the second category. The disease was categorized by lesions of the eyelid margins and gradually developing lesions at the superior corneoscleral limbus in both eyes. One of the corneal lesions was excised and was found to be composed of subepithelial infiltrates of eosinophils, foam cells, and characteristic Touton giant cells. Xanthoma disseminatum is apparently not a hereditary disease and is not associated with disorders of lipid or cholesterol metabolism. The lesions of xanthoma disseminatum respond poorly to chemotherapy and radiation in contrast to the Langerhans' cell disorders of Group 1. (2 figures, 1 table, 27 references)—David Shoch

Archives of Neurology

Eye movement abnormalities as a predictor of the acquired immunodeficiency syndrome de-

mentia complex. Currie, J., Benson, E., Ramsden, B., Perdices, M., and Cooper, D. (Neurophysiol. and Neurovisual Res., Mental Health Res., Inst. of Victoria, Private Bag No. 3, Parkville, Melbourne, Victoria 3052, Australia). Arch. Neurol. 45:949, 1988.

It has been estimated that five years after infection with the human immunodeficiency virus, 30% of those infected will develop the syndrome. The most common neurologic complication of human immunodeficiency virus (HIV) infection in these patients is the AIDS dementia complex, manifest as a progressive dementia accompanied by motor and behavioral disturbances. This syndrome has been estimated to occur in at least two thirds of the patients with AIDS. To attempt to identify a marker for the dementia complex, the authors used infrared oculography to record eye movements in a group of patients with AIDS, some of whom had the AIDS dementia complex. Seven of seven patients with some degree of the AIDS dementia complex and six of seven patients who were HIV-positive showed abnormalities of eye movements, including saccadic and smooth pursuit function, the severity of which correlated strongly with the severity of the dementia. Monitoring eye movements may be a useful noninvasive technique to detect neurologic dysfunction in asymptomatic patients who are seropositive for HIV. These findings may also serve as a guide to antiviral therapy, particularly in monitoring the neurologic response to treatment with antiviral agents. (3 figures, 36 references)—David Shoch

Lithium-induced downbeat nystagmus. Williams, D. P., Troost, T., and Rogers, J. (Dept. Neurol., Bowman Gray School of Med. of Wake Forest Univ., 300 S. Hawthorne Rd., Winston-Salem, NC 27103). Arch. Neurol. 45:1022, 1988.

Two patients treated with lithium for psychiatric illness developed downbeat nystagmus in the primary position. After stopping the lithium, one patient had a complete resolution of this nystagmus and the other had only a small improvement. Valproate sodium helped to suppress the nystagmus in the second patient. (2 figures, 14 references)—David Shoch

British Journal of Ophthalmology

Photostress recovery in chronic open angle glaucoma. Sherman, M. D., and Henkind, P. (Dept. Ophthalmol., Univ. Arizona Health Sci. Ctr., Tucson, AZ 85724). Br. J. Ophthalmol. 72:641, 1988.

The authors used a halogen bulb of an ophthalmoscope to stress the macula for ten seconds in 30 glaucomatous eyes (15 patients). A similar test was performed on 30 normal control eyes. Average recovery time was 74.7 ± 35.39 seconds in eyes with glaucoma and 41.97 ± 17.34 seconds in control eyes ($P < .001$). There was no correlation between age and recovery time or between visual acuity and recovery time for either group. There was no connection between intraocular pressure and recovery time for the glaucoma group. The size of the pupil was not controlled in this study, but it was not considered an important factor since only the macula was being stressed and not the peripheral retina. Delayed recovery occurs with damage to any of the layers of the retina and choroid in the macular area. The pathophysiologic basis for delayed photostress recovery in patients with glaucoma remains unexplained. (2 figures, 3 tables, 13 references)—David Shoch

Birdshot chorioretinopathy. Clinical characteristics and evolution. Priem, H. A., and Oosterhuis, J. A. (Dienst Oogheelkunde, Academisch Ziekenhuis, De Pintelaan 185, 9000 Gent, Belgium). Br. J. Ophthalmol. 72:646, 1988.

During the period 1980-6 102 patients from 14 European eye clinics were diagnosed as having birdshot chorioretinopathy (BSCR). All were Caucasian, and the series consisted of 47 men and 55 women, with a mean age of 52.5 years. The major findings in this rare disorder concern the ocular fundus. Most marked are the patterned distribution of depigmented spots without hyperpigmentation, radiation from the optic disc in association with vitritis, retinal vasculopathy with frequent cystoid macular oedema, and involvement of the optic nerve head. The distribution and appearance of the lesions suggest that they are related to the major choroidal veins. Complications of the disease were epiretinal membranes, retinal neovascularization, recurrent vitreous hemorrhage, subretinal neovascular membranes oc-

curring both in the juxtapapillary and macular regions, and optic atrophy. The medical history was not contributary. HLA testing showed very strong disease association with HLA A29 (95.8%). The evidence suggests that it is a single disease entity rather than a group of disorders because of the remarkable similarity in the ophthalmological appearance and the clinical course, combined with the exceptionally high association with HLA A29. (6 figures, 10 tables, 22 references)—Authors' abstract

Vitrectomy for idiopathic epiretinal membranes causing macular pucker. De Bustros, S., Thompson, J. T., Michels, R. G., Rice, T. A., and Glaser, B. M. (Maumenee 115, 600 N. Wolfe St., Baltimore, MD 21205). Br. J. Ophthalmol. 72:692, 1988.

Abnormal epiretinal membranes were removed in 70 consecutive eyes during vitrectomy. Vision improved in 61, was unchanged in six, and was worse in three eyes. However, in 38 of 60 phakic eyes with improved vision initially, vision gradually decreased because of the development of cataracts, primarily nuclear sclerosis. In general, better results were obtained if the initial visual acuity was 20/100 or better and if the duration of blurred vision was short. The prognosis was also better in eyes in which the membrane was thin and cellophane-like. The presence of a posterior traction retinal detachment made the prognosis poorer. (3 figures, 1 table, 10 references)—David Shoch

Addition of hyaluronidase to lignocaine with adrenaline for retrobulbar anaesthesia in the surgery of senile cataract. Thomson, I. (Agogo Hosp., P.O. Box 27, Agogo, Ghana). Br. J. Ophthalmol. 72:700, 1988.

In a study on 150 patients undergoing intracapsular cataract extraction, the author randomly administered a retrobulbar mixture of either 2% lignocaine with adrenaline or the same mixture plus 1,500 units of hyaluronidase per milliliter. The identity of the mixtures was masked to the surgeon. At the end of the series the code was broken and it was found that 92% of the eyes that received blocks including hyaluronidase were judged successful, whereas only 56% of the eyes that received blocks with no hyaluronidase were successful ($P < .01$). (3 tables, 7 references)—David Shoch

Journal of the Royal Society of Medicine

The ocular signs and complications of epidermolysis bullosa. McDonnell, P. J., and Spalton, D. J. (South Wing Eye Dept., St. Thomas' Hosp., London, England SE1 7EH). J. R. Soc. Med. 81:576, 1988.

Epidermolysis bullosa is a group of blistering diseases of the skin which occur after minor degrees of trauma. They are believed to be hereditary. The type most often associated with ocular disease is dystrophic epidermolysis bullosa, in which the separation occurs at the level of the lamina lucida layer of the epidermal basement membrane. Of 11 patients with this disease, eight had ocular findings. The most common abnormalities were symblepharon (six patients) and limbal broadening with large avascular areas of the superior and inferior corneoscleral limbus (five patients). Two patients had a stromal opacity at the level of Bowman's membrane. (6 figures, 10 references)—David Shoch

International Ophthalmology

The ocular ischemic syndrome. Brown, G. C., and Magargal, L. E. (910 E. Willow Grove Ave., Wyndmoor, PA 19118). Int. Ophthalmol. 11:239, 1988.

The authors reviewed the records of 43 consecutive patients (51 eyes) with ocular symptoms attributable to severe carotid artery obstruction. The average patient age was 64 years. The most common abnormal finding in the anterior segment was neovascularization of the iris (two thirds of the eyes). Midperipheral retinal hemorrhages were seen in 80% of the eyes, and posterior segment neovascularization was seen in about one third. Fluorescein angiography showed delayed choroidal and retinal filling and electroretinography demonstrated reduced A and B waves. About half of the patients had systemic hypertension and just less than half were diabetic. Almost one

quarter of the patients had had a cerebrovascular accident. When the ocular ischemia was unilateral, there was an ipsilateral stenosis of at least 80% in the internal or common carotid system. Of eight patients who had bilateral ocular ischemia, 100% stenosis of one internal carotid artery and a contralateral stenosis of at least 50% was present in six. (13 figures, 4 tables, 25 references)—David Shoch

Neurology

Infarction of abducens nerve fascicle as cause of isolated sixth nerve palsy related to hypertension. Donaldson, D., and Rosenberg, N. L. (Neurol. Ser., 127, Vet. Admin. Med. Ctr., 1055 Clermont St., Denver, CO 80220). Neurology 38:1654, 1988.

A 61-year-old man experienced an episode of horizontal diplopia because of a complete left sixth nerve palsy. The results of ophthalmologic and neurologic examinations were normal. Computed tomography showed a 5 × 8-mm, well-defined, low-density lesion of the left mid pons between the fourth ventricle and the cerebral aqueduct near the midline. This was believed to be an infarction. There was no evidence of aneurysms, extraorbital masses, or any other abnormality of the superior orbital fissure. Four months later there was complete resolution of the palsy. Thus, it would appear that isolated abducens palsy can result from a small pontine infarction that involves the abducens nerve fascicle but does not damage surrounding tissue. The authors recommend radiologic study of isolated abducens nerve palsy, particularly in individuals with systemic vascular disease. (1 figure, 5 references)—David Shoch

Ophthalmologica

Corneal endothelial cell density after trabeculoplasty. Rouhiainen, H., and Kemppinen, P. (Eye Dept., Univ. Center, Hospital of Kuopio, SF-70210 Kuopio, Finland). Ophthalmologica 196:182, 1988.

The authors performed argon laser trabeculoplasty on 70 eyes. In each eye they placed 50 burns evenly distributed around 180 degrees of the anterior border of the pigmented trabecular band. Of the 70 eyes, 29 had had previous argon laser trabeculoplasty. Eighteen glaucomatous fellow eyes not treated were used as controls. Ten photographs of the endothelial cells were taken 12 to 18 months postoperatively of each eye. In the control eyes the mean endothelial cell density was 1,831 ± 275 cells/mm^2; in the treated eyes it was 1,753 ± 309 cells/mm^2. This difference was not statistically significant. The amount of energy delivered as well as patient age had no impact on the cell density. (1 figure, 10 references)—David Shoch

Influence of age on the transparency of the lens in normals. A population study with help of the Lens Opacity Meter 701. De Natale, R., Flammer, J., Zulauf, M., and Bebie, T. (Univ. Eye Clin., Mittlere Strasse 91, CH-4056 Basel Switzerland). Ophthalmologica 197:14, 1988.

The authors used a Lens Opacity Meter, which projects a dark red beam 1.5 mm in diameter at a wavelength of 700 nm into the eye along the optic axis. The instrument has a sensor that measures the back scatter from the lens to the instrument. The study subjects included 266 healthy volunteers (485 eyes) who ranged in age from 7 to 86 years. There was no clinical evidence of cataract by slit-lamp examination and visual acuity was 20/25 or better in all patients. The authors showed that the light scatter from the human lens increased continuously with patient age. Up to the age of 45 years the relationship could be represented by a linear regression, but above the age of 65 years there was a sharp upward trend of the opacity and the whole curve was better represented by a quadratic equation. This study established a normal baseline and might be useful for quantifying changes in opacity over time. (9 figures, 11 references)—David Shoch

NEWS ITEMS

Send News Items to
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The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length. Announcements of meetings and courses must be received at least four months before the event.

Catholic University of Rome: International Workshop on Retinopathy of Prematurity

An International Workshop on Retinopathy of Prematurity will be held at the Catholic University of Rome, June 30 and July 1, 1989, in Rome, Italy. For further information, write Benedetto Ricci, M.D., Dept. of Ophthalmology, Catholic University, Largo F. Vito - 00168 Rome, Italy.

Harvard Medical School and Massachusetts Eye and Ear Infirmary: Third Annual Meeting

The Harvard Medical School and Massachusetts Eye and Ear Infirmary will sponsor the Third Annual Meeting: Selected Topics in Ophthalmology, Feb. 5–9, 1989, in Puerto Vallarta, Mexico. For further information, write Bernice McPhee, Director, Department of Education Services, Massachusetts Eye and Ear Infirmary, 243 Charles St., Boston, MA 02114.

Scripps Memorial Hospital: Visions in Ophthalmology '89

Scripps Memorial Hospital will sponsor Visions in Ophthalmology '89 in San Diego, California, April 1, 1989. For further information, write Nomi Feldman, Conference Coordinator, 3770 Tansy St., San Diego, CA 92121.

Wills Eye Hospital: Fourteenth Annual Ophthalmology Review Course

Wills Eye Hospital will sponsor the Fourteenth Annual Ophthalmology Review Course, March 18–22, 1989, in Philadelphia, Pennsylvania. For further information, write Lucia M. Manes, Department of Continuing Medical Education, Wills Eye Hospital, 9th and Walnut Sts., Philadelphia, PA 19107.

Manhattan Eye, Ear & Throat Hospital: The Masters of Ophthalmic Plastic Surgery

Manhattan Eye, Ear & Throat Hospital will sponsor a course, The Masters of Ophthalmic Plastic Surgery, March 10 and 11, 1989, in New York, New York. For further information, write Ophthalmology Course Coordinator, Manhattan Eye, Ear & Throat Hospital, 210 E. 64th St., New York, NY 10021.

University of Tennessee: Eighteenth Annual Residents-Alumni Day

The University of Tennessee will sponsor the Eighteenth Annual Residents-Alumni Day, March 10, 1989, in Memphis, Tennessee. For further information, write Roger L. Hiatt, M.D., Department of Ophthalmology, University of Tennessee, 956 Court Ave., Memphis, TN 38163.

Wills Eye Hospital: Forty-first Annual Conference

Wills Eye Hospital will hold its Forty-first Annual Conference, March 9–11, 1989, in Philadelphia, Pennsylvania. For further information, write Jeanne E. Coughlin, Meeting Manager, 1621 Norristown Rd., Maple Glen, PA 19002.

Francis I. Proctor Foundation for Research in Ophthalmology: Ophthalmology in the Third World: A Practical Orientation

The Francis I. Proctor Foundation for Research in Ophthalmology will sponsor a meeting, Ophthalmology in the Third World: A Practical Orientation, March 8–10, 1989, in San Francisco, California. For further information, wirte Haas Foundation, c/o Proctor Medical Group, 95 Kirkham St., San Francisco, CA 94122.

University of Michigan Medical School: Recent Advances in Cornea, External Disease, and Cataract: 61st Annual Ophthalmology Spring Conference

The University of Michigan Medical School will sponsor a course, Recent Advances in Cornea, External Disease, and Cataract: 61st Annual Ophthalmology Spring Conference, May 19 and 20, 1989, in Ann Arbor, Michigan. For further information, write Betty Phillips, Program Assistant, Office of Continuing Medical Education, Towsley Center, Box 0201, University of Michigan Medical School, Ann Arbor, MI 48109-0201.

National Society to Prevent Blindness: 1989 Burroughs Wellcome Research Fellowship

The National Society to Prevent Blindness will administer a Burroughs Wellcome Research Fellowship in ophthalmology to begin July 1, 1989. The fellowship is aimed at providing research training in a basic science related to ophthalmology to a physician who has completed a residency in ophthalmology. It provides an annual stipend of $22,000 and $2,000 for laboratory expenses and travel incidental to fellowship training, with an optional second-year extension.

The deadline for applications is May 1, 1989. Applications should be sent to National Society to Prevent Blindness, 500 E. Remington Road, Schaumburg, IL 60173, Attention: Research Committee.

Fight for Sight, Inc.: Scientific Awards 1988–1989

Mildred Weisenfeld, Founder and Executive Director of Fight for Sight, Inc. announced that 13 grants-in-aid, 12 postdoctoral research fellowships, continued support to four Fight for Sight Pediatric Eye Clinics, and a special award for the establishment of a Laser Unit have been approved for 1988–1989 by the Fight for Sight Research Award Program, administered by the Association for Research in Vision and Ophthalmology.

Grants-in-Aid

Robert S. Baker, M.D., Dept. of Ophthalmology, University of Kentucky (Lexington, KY), "Surgical reinnervation of paretic extraocular muscle," (In Memory of Dr. Herman M. Burian and wife, Gladys), $9,000.

Janis T. Eells, Ph.D., Dept. of Pharmacology & Toxicology, Medical College of Wisconsin (Milwaukee, WI), "The mechanism of methanol induced ocular toxicity," $9,000.

Federico Gonzalez-Fernandez, M.D., Dept. of Pathology, University of Virginia (Charlottesville, VA), "Rat interstitial-retinol binding protein: Molecular cloning and gene expression," (In Memory of Mary E. and Alexander P. Hirsch), $9,000.

Maria Hadjiconstantinou-Neff, M.D., Dept. of Pharmacology, Ohio State University (Columbus, OH), "Excitatory amino acids and diabetic retinopathy," (In Honor of Bob Hope), $9,000.

Mark J. Kupersmith, M.D., Depts. of Neurology and Ophthalmology, New York University Medical Center (New York, NY), "Dopaminergic influences on human visual function," $9,000.

Nancy J. Mangini, Ph.D., Dept. of Ophthalmology, University of Illinois (Chicago, IL), "Effects of mellaril on cultured retinal pigment epithelial (RPE) cells," (Supported by the Herman B. and Albert G. Mosler Memorial Fund), $9,000.

Todd P. Margolis, M.D., Dept. of Ophthalmology, University of California (San Francisco, CA), "Intracellular pathways of axonal transport of herpes simplex virus," (Supported by a grant from Burroughs Wellcome Fund), $8,000.

Baruch Minke, Ph.D., Dept. of Neuroscience, Johns Hopkins University (Baltimore, MD), "Light-activated photoreceptor currents of *Drosophila* mutants measured with patch electrode," $9,000.

Ling Yu Shih, M.D., Dept. of Pediatrics, Uni-

versity of Medicine & Dentistry of New Jersey (Newark, NJ), "Congenital cataract and maternal galactose metabolism," $5,000.

Marc J. Siegel, M.D., Dept. of Ophthalmology, Mt. Sinai Medical Center (New York, NY), "Muramyl dipeptide in glaucoma filtering surgery in monkeys," $9,000.

Om P. Srivastava, Ph.D., Dept. of Biochemistry, Missouri Lions Eye Research Foundation (Columbia, MO), "Surface receptors for polypeptide growth factors in corneal endothelial cells," $9,000.

Anand Swaroop, Ph.D., Dept. of Human Genetics, Yale University (New Haven, CT), "Isolation of candidate cDNAs for X-linked ocular diseases using a novel strategy," $9,000.

Marco A. Zarbin, M.D., Dept. of Ophthalmology, Johns Hopkins University (Baltimore, MD), "Localization of central and peripheral benzodiazepine receptors in rat and human retina," $5,690.

Postdoctoral Research Fellowships

Marc S. Cohen, M.D., Wills Eye Hospital (Philadelphia, PA), (Peter J. Savino, M.D., Sponsor), "Visual dysfunction in children with neurofibromatosis," $12,000.

Ziming Dong, M.D., Depts. of Ophthalmology, Neurosciences, & Medicine, University of Medicine & Dentistry of New Jersey (Newark, NJ), (Leonard Bielory, M.D., and Larry Frohman, M.D., sponsors), "Prospective immunological evaluation of optic neuritis," $12,000.

Randy H. Kardon, M.D., Dept. of Ophthalmology, University of Iowa (Iowa City, IA), (H. Stanley Thompson, M.D., Sponsor), "Objective pupil perimetry," $12,000.

Chen-Ching Lai, Ph.D., Dept. of Pathology, University of California (La Jolla, CA), (Wen-Hwa Lee, Ph.D., Sponsor), "Oncogenic suppression activity of human retinoblastoma gene," $12,000.

Thomas F. Mauger, M.D., Dept. of Ophthalmology, Ohio State University (Columbus, OH), (Curtin G. Kelley, M.D., Sponsor), "Corneal physiologic changes with alloplastic intracorneal implants," $12,000.

Mary Jo Sagaties, Ph.D., Dept. of Ophthalmology, New England Medical Center Hospitals (Boston, MA), (Bernard Schwartz, M.D., Sponsor), "Three-dimensional analysis of pallor of the optic disc," $12,000.

Gerald G. Striph, M.D., Dept. of Ophthalmology, Johns Hopkins University (Baltimore, MD), (Neil R. Miller, M.D., Sponsor), "Cytoskeletal protein gene expression in the retinal ganglion cell," (In Honor of Dr. Charles A. Perera), $12,000.

Rita L. Storch, M.D., Dept. of Neurology, Mount Sinai School of Medicine (New York, NY), (Ivan Bodis-Wollner, M.D., Sponsor), "Longitudinal evaluation of pattern electroretinogram (PERG) in the early detection of glaucoma," (In Memory of Mary E. and Alexander P. Hirsch), $12,000.

Rohit Varma, M.D., Wills Eye Hospital (Philadelphia, PA), (George L. Spaeth, M.D., Sponsor), "Optic disc analysis," $12,000.

Naheed Wali, Ph.D., Dept. of Ophthalmology, Children's Hospital (Columbus, OH), (Lawrence E. Leguire, Ph.D., Sponsor), "Contrast sensitivity functions in pediatric ophthalmology," $12,000.

Lee A. Wiley, M.D., Dept. of Ophthalmology, University of Pittsburgh (Pittsburgh, PA), (Nirmala Sundar-Raj, Ph.D., Sponsor), "Immunohistochemical analysis of normal and diseased human limbal epithelium," (In Memory of Silas Adelsheim), $12,000.

Samuel C.-H. Yiu, Ph.D., Eye Research Institute, Harvard University (Boston, MA), (Darlene A. Dartt, Ph.D., Sponsor), "Role of protein kinases in lacrimal gland fluid secretion," $12,000.

Service Projects

The Board of Directors of the organization approved renewal support to four Fight for Sight Pediatric Eye Clinics:

Columbia-Presbyterian Medical Center, New York City, Howard M. Eggers, M.D., Director, $3,200.

Eye Institute of New Jersey, Newark, Anthony R. Caputo, M.D., Director, $12,000.

Children's Hospital of the University of Pittsburgh, David Hiles, M.D., Director, $3,500.

Wills Eye Hospital, Philadelphia, Joseph Calhoun, M.D., Director, $14,736.

Special Award

Wills Eye Hospital, Philadelphia, Raymond E. Adams, M.D., establishment of a Laser Unit for the treatment of a variety of vascular diseases of the retina, with emphasis on young diabetics (funded by the Fight for Sight of Greater Philadelphia), $32,500.

Personals

Norman E. Byer

Norman E. Byer has been awarded the Wacker Prize for his clinical research on the natural history of peripheral retinal degenerations. The prize is funded by the Hermann Wacker Foundation of Munich, West Germany, and is awarded every two years by the Club Jules Gonin. The award was presented in September in Brugge, Belgium at the biennial meeting of the Club Gonin.

Howard Schatz

Howard Schatz was presented with the Fifth Arlo A. Morrison Lecture Award by the California Association of Ophthalmology, Sept. 10, 1988, in Monterey, California.

Alfred Sommer

Alfred Sommer has received the 1988 Charles A. Dana Award for Pioneering Achievement in Health and Higher Education. The award was made Nov. 2, 1988, by the Center for the Study of Philanthropy, City University of New York. Dr. Sommer was cited for his successful strategy for combating vitamin A deficiency that leads to blindness and death in children in developing countries. His work has led to the implementation of international preventive health programs by WHO and the United Nations Food and Agricultural Organization.

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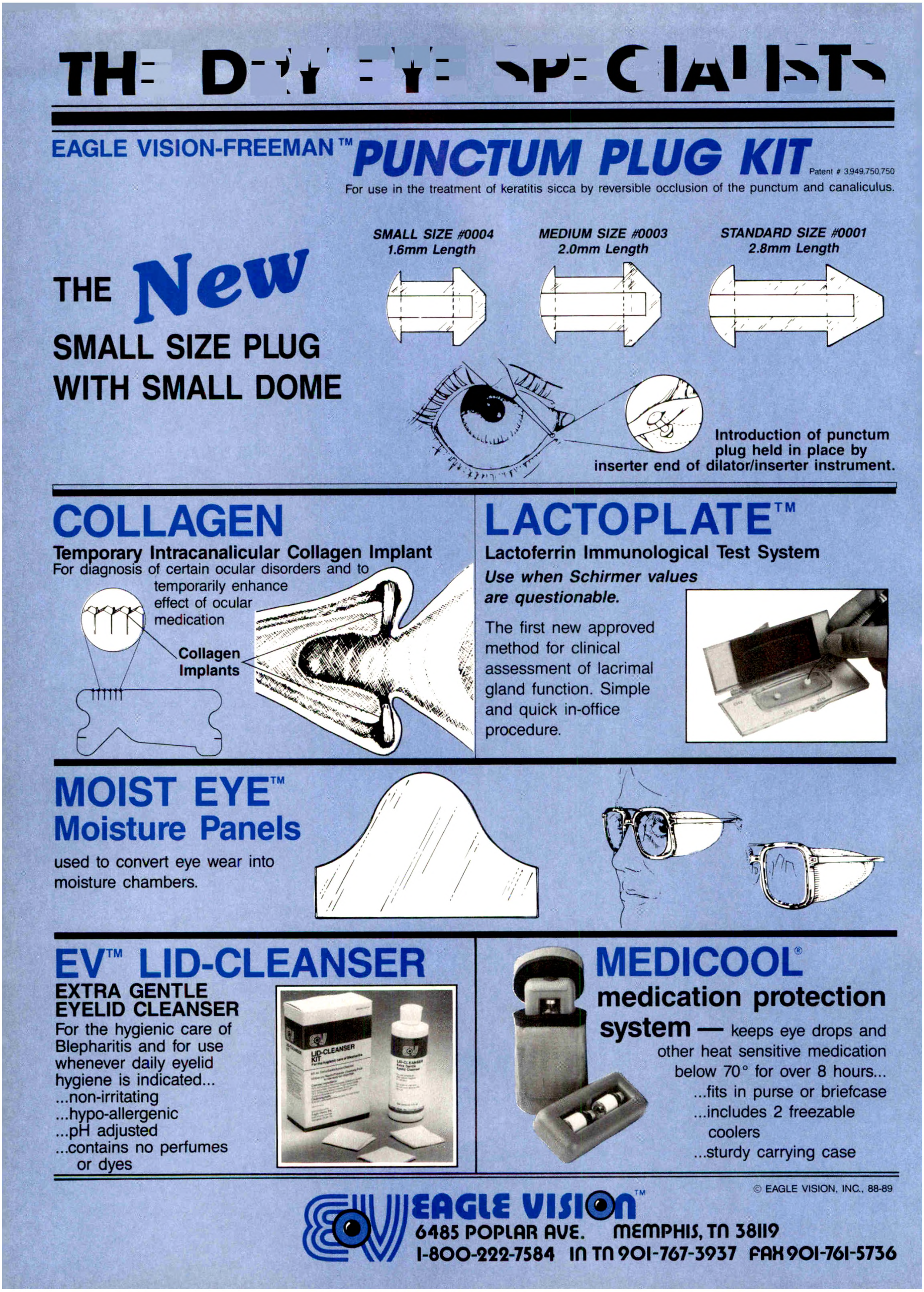
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Use 8 1/2 × 11-inch heavy, white, bond paper.

Provide 1 1/2-inch margins on all four sides of each page and indent paragraphs one-half inch.

The entire typescript, including title page, quotations, footnotes, acknowledgment, references, legends, and tables, must be double-spaced.

Use black, clearly legible type.

Use block type.

Do not underline.

Do not use italics or boldface.

Do not use all capitals.

Do not justify right margins.

Do not use a dot matrix printer. The type must be letter quality with clear, unbroken characters that do not touch or overlap.

Do not use any single-spacing.

Do not use condensed type.

Number each page in the upper right-hand corner. List the first author's name and short title (maximum, 60 characters and spaces) in the upper right-hand corner.

Spell out all terms except standard measurements, such as mm Hg, cm, and ml, used with numeric quantities; R.E. and L.E. may be used. Do not abbreviate IOP, CME, RPE, and the like, or use acronyms (BARD, ARN, ROP).

If percentages are used, the numerical equivalents must be included, for example, Of 80 patients, 20 (25%) had retinitis pigmentosa.

Prepare references, legends, and tables in THE JOURNAL form. (See following detailed instructions.)

Original Articles

The manuscript should be arranged in the following order: (1) Title page; (2) Summary; (3) Introductory text; (4) Material and Methods or Case Reports; (5) Results; (6) Discussion; (7) References; (8) Legends for illustrations; (9) Tables.

Title page—The title page is page 1. It should contain the title, a brief heading (no more than

60 characters and spaces) in the upper right hand corner, and each author's name with the highest (one only) academic degree. The department and the institution where the study was performed should be indicated. Sponsoring organizations and grants are acknowledged on the title page.

Referring physicians, consultants, editorial assistants, photographers, artists, laboratory assistants, secretaries, and others who assist in preparation of a paper cannot be acknowledged however valuable their services.

The name and mailing address of the author to whom requests for reprints should be directed must be indicated.

Each page that follows the title page must be numbered consecutively, and must include the first author's name and the brief title in the upper right-hand corner.

Summary—Each article must have a summary that synthesizes specifically the content of the paper in no more than 150 words. It should include the main clinical or research data and findings but exclude speculation. The summary must be written so that the message of the full paper can be understood independently. It must not contain references, illustrations, tables, or data not included in the full text. It should not repeat or paraphrase the title. The summary should answer the questions: who or what was studied, why the study was done, the results, and the significance of the study.

Narration—Articles should be organized and prepared in the style used by THE JOURNAL. A brief introductory statement of the problem should be presented. Material and methods or the patient selection should then be precisely and clearly described in enough detail for a reader to replicate the study. Results of the study should be given, followed by a discussion. The discussion elucidates the results and must relate directly to the topic of the paper.

References—THE JOURNAL does not publish extensive bibliographic reviews. References must be numbered consecutively, both in the text and in the reference list. The author is responsible for complete and accurate references, including the proper capitalization and accent marks used in foreign-language publications.

Personal communications, posters, program abstracts, unpublished data, and oral discussions that the reader cannot retrieve should be kept to a minimum and must be incorporated into the text without reference numbers. References to studies that have been accepted but have not yet been published must indicate the publication in which they will be published. Primary, not secondary, sources must be cited. References to books must contain inclusive pages of the section cited. The names of all authors must be cited in the reference list. THE JOURNALdoes not use the term et al. The following style is used by THE JOURNAL for periodicals (1), for books (2), and for chapters in books (3).

1. Rinkoff, J., Machemer, R., Hida, T., and Chandler, D.: Temperature-dependent light damage to the retina. Am. J. Ophthalmol. 102:452, 1986.
2. Helveston, E. M.: Atlas of Strabismus Surgery, 3rd ed. St. Louis, C. V. Mosby, 1985, p. 156.
3. O'Connor, G. R.: Herpes zoster uveitis. In Kraus-Mackiw, E., and O'Connor, G. R. (eds.): Uveitis. Pathophysiology and Therapy. New York, Thieme-Stratton, 1983, pp. 56–65.

The originator of the personal communication must provide written permission to be quoted.

Abbreviations for periodicals are listed in Index Medicus: Am. J. Ophthalmol., Surv. Ophthalmol., Br. J. Ophthalmol., and the like. If there is any doubt about an abbreviation, the full name of the publication should be spelled out completely.

Illustrations—Graphs, diagrams, and photographs must not be mounted. Each illustration should be numbered and cited consecutively in the text. The illustration number, an arrow indicating the top of the picture, and the first author's name should be indicated on a label on the back.

The figure number, legend, or text should not appear on the face of an illustration.

Graphs, diagrams, and line drawings must be prepared by a professional artist on heavy white paper with India ink. Lighter lines should be used for axes than for data curves. Photographs must have a glossy finish and a sharp contrast. Lettering, arrows, and the like must be professionally applied. In a series of illustrations, all parts should be oriented in the same direction. Photographs should be the same size or slightly larger than the intended reproductions. Figure widths in The Journal are 3 inches (one column) and 6 ½ inches (two columns). Lettering must be planned with reductions to these sizes in mind; letters should be of uniform size and large enough to be read easily after reduction.

Cropping should be done to exclude nonpertinent material from photographs. The front

surface of each photograph should be marked with a grease pencil to show the area to be reproduced.

THE JOURNAL does not use stereoscopic illustrations.

Each illustration must have a descriptive legend. Legends should be typed consecutively on a page (separate from the illustrations themselves). Legends should be typed in the form used by the THE JOURNAL, as follows:

Fig. 1 (Jones, Smith, and Brown). Histologic section of the eye (hematoxylin and eosin, ×70).

If there are more than three authors, use Jones and associates.

If identifiable photographs of patients are submitted the author must supply THE JOURNAL with proof of informed consent.

Individual illustrations and legends are preferred to composites made up of two or more separate parts. If multiple-part illustrations are submitted, they should be labeled from left to right and from top to bottom as follows:

Fig. 1 (Jones, Smith, and Brown). Case 3. Top left, The patient preoperatively. Top right, Three days after surgery. Bottom left, Four months after surgery. Bottom right, One year after surgery.

Do not label composite illustrations with letters (for example, part A, part B, . . .). Composite figures must be planned with the dimensions of a JOURNAL page and the need for a legend considered.

The visual field charts used in THE JOURNAL will be supplied to authors on request without charge. Write to Editorial Administrative Assistant, American Journal of Ophthalmology, Tribune Tower, Suite 1415, 435 N. Michigan Ave., Chicago, IL 60611.

Color—Authors must contribute to the cost of color reproductions. The charge to authors for color is $500 per page of color. Both color transparencies and high-quality color prints must be submitted with the paper, together with a layout indicating the proposed distribution of the illustrations and legends.

Tables—Each table must have a title, be numbered with an arabic numeral, and be cited consecutively in the text.

Each table must be double-spaced and nothing in the table should be underlined. Photographically reproduced or reduced tables are not acceptable.

The first line of a table should have the table number. The second line should have the title of the table.

Vertical lines should not be used anywhere in the table.

All columns should be labelled; lengthy descriptions belong in the text or as a footnote to the table, not in the table itself. Tables should be used only for summarizing numeric data.

Abbreviations should be avoided. If necessary, they must be fully explained in a footnote. The following symbols are used for footnotes in the order indicated: * (asterisk), † (dagger), ‡ (double dagger), § (section mark), ‖ (parallels), ¶ (paragraph mark), and # (number sign).

Proofs—A copy of the edited typescript is sent to the corresponding author. Author corrections must be entered in red ink. Each author query must be answered. Corrections are minimized by careful initial preparation of the manuscript.

The typescript must be returned to the Manuscript Editor, Ophthalmic Publishing Company, Suite 1415, 435 N. Michigan Ave., Chicago, IL 60611, within 48 hours of receipt. Failure to return the typescript promptly delays publication.

Reprints—Reprints must be ordered promptly. A reprint order form is sent to the submitting author four to six weeks before publication of the article.

Letters to THE JOURNAL

Letters describe unusual clinical or pathologic findings, experimental results, and new instruments and techniques. Letter typescripts should be prepared in the same way as Original Articles. They must be no more than five pages in length (title page, two pages of text, reference page, and legend page). References must be limited to five. No more than two black-and-white illustrations, 3 inches wide (one column in width), may be used. Color illustrations cannot be used.

The Editorial Board either accepts or rejects letters. They are not returned with suggestions for revision. Since these instructions markedly limit the opportunity for an extended discussion or review, THE JOURNAL does not publish correspondence concerning letters.

Correspondence

Correspondence concerning recent articles or other material published in THE JOURNAL should be submitted within six weeks of publication. Correspondence typescripts should be prepared in the same way as an Original Article

and should be no more than two typewritten pages in length. Every effort will be made to resolve controversies between the correspondents and the authors of the article before formal publication.

News Items

THE JOURNAL welcomes information concerning meetings, honors, and appointments. Only one new item should be included on each page. News items should be double-spaced and provide the name and address of the responsible author.

Source Texts

THE JOURNAL recommends the following publications as guides to style, grammar, and spelling:

CBE Style Manual Committee: Council of Biology Editors Style Manual. A Guide for Authors, Editors and Publishers in the Biological Sciences, 5th ed. Bethesda, Council of Biology Editors, 1983.

The Chicago Manual of Style, 13th ed. Chicago, University of Chicago Press, 1982.

Strunk, W., Jr., and White, E. B.: The Elements of Style, 3rd ed. New York, Macmillan Publishing Co., 1979.

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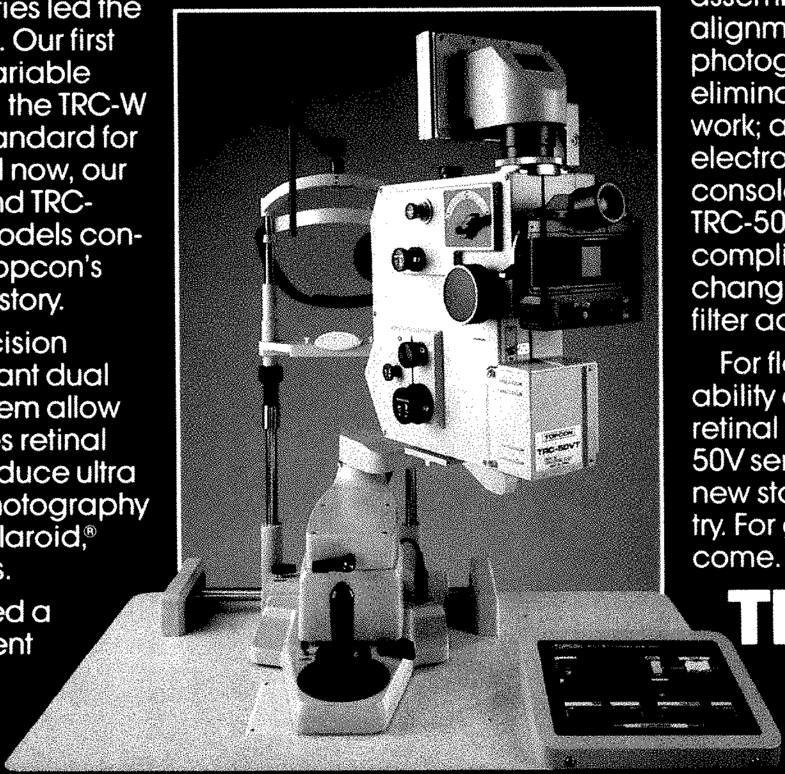


NEW PRODUCTS AND SERVICES

New products and services considered by the editors to be of interest to our readers are described on the basis of information supplied by the companies cited. Publication of these notices does not imply endorsement or warranty by The Ophthalmic Publishing Company, publishers of The American Journal of Ophthalmology, for these products and services.

Surgical Equipment

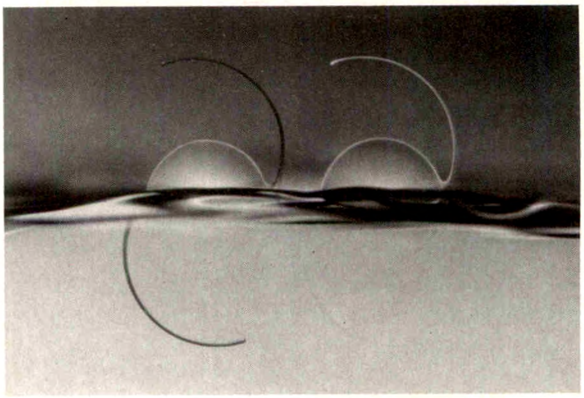
Gerber Optical
30 S. Satellite Rd.
South Windsor, CT 06074
Tel: (203) 282-2020

Gerber Optical has introduced a microprocessor-controlled edger designed for dry cutting operation on CR-39, polycarbonate, and high-index lenses. The accurate geometry data needed to direct the LE-3 originates from a Gerber Frame Tracer, eliminating the need for patterns. Data may come directly from the Frame Tracer or through an intermediate storage computer. Operation of the edger is simple, requiring only entry of a job number (by bar code wand or keyboard) and loading of the lens. After that, all edging operations are automatic, including roughing, finishing, beveling, and pin beveling.

The LE-3 uses a three-dimensional probing process that precedes the edging cycle. The information captured in this quik-map operation allows the system to place the bevel, wire groove, and pin bevels without trial and error or operator intervention. While the edging cycle is completely automatic, the LE-3's built-in computer accommodates the widest possible range of jobs. Set-up parameters include choice of bevel location, lens material, and size adjustment.

Intraocular Lenses

Iolab Corp.
500 Iolab Dr.
Claremont, CA 91711
Tel: (714) 624-2020



Iolab Intraocular, a division of Iolab Corp., announced the availability of a new series of lenses: EZVUE one-piece lenses with violet haptics. These lenses provide better visualization during insertion. They will also aid the surgeon in placing both haptics in the capsule. The deep violet color of the EZVUE haptic is the same stable, nontoxic color that is used in Vicryl absorbable ophthalmic sutures.

The EZVUE lenses offer the identical haptic flexibility and performance as equivalent clear haptic lenses. These large optic, lathe-cut violet haptic lenses are now available in a variety of styles. They are also enhanced by the Class I, ultraviolet-absorbing feature, UVBLOC Plus.

Storz Ophthalmics, Inc.
1365 Hamlet Ave.
Clearwater, FL 34616
Tel: (813) 441-3556

Storz Ophthalmics, Inc. announced that two of its newest Coburn one-piece, polymethylmethacrylate-absorbing lenses, the 94-KUV and the P004-UV, have been recommended by the Food and Drug Administration Ophthalmic Panel for premarket approval. These lenses were designed by Charles D. Kelman, M.D., and are manufactured using Plexiglas UF3. These posterior chamber lenses feature a new triple-fulcrum haptic design that works in tandem with the gently tapered optic to give surgeons extra flexibility and ease of implantation. A narrow incision profile enables these lenses to clear even a small pupil, allowing for a reduction in the size of the incision.


PHACO 3000™ LINEAR
UNITED SONICS PUTS MORE PHACO CAPABILITY IN YOUR HANDS FOR LESS.
Looking for small-incision surgical equipment with full linear power? Look into the new Phaco 3000™ Linear.
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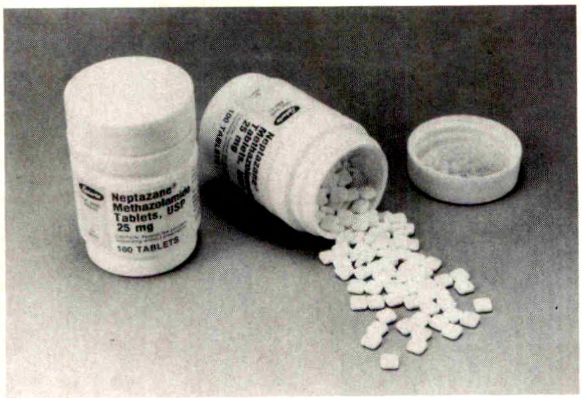
SELECT
PANEL
FOOT SW
Besides linear capability, you also get a small, lightweight autoclavable handpiece. Increased stroke length. Automatic tuning circuitry. And the ability to easily adapt to the I/A of your choice.*
Here's more good news. The new Phaco 3000L costs substantially less than other systems. So, combined with United Sonics' DRG-responsive reusable needles and sleeves, you make a major transition without a major investment. And our highly trained equipment and surgical specialists make sure the transition is a smooth one.
To arrange a surgical evaluation, call United Sonics, toll-free, at 1-800-874-1133 (in New York, 516-434-8800) or use our TWX number, 510-224-6182.
UNITED SONICS
180 Vanderbilt Parkway, Hauppauge, NY 11788
*Call United Sonics for information on the Phaco 3000 series system compatible with your I/A. The Phaco 3000L is compatible with: CooperVision's Cavitron 6000, 6500, 7000, 7500, 8000; System VI™; and Ocutome® II — Coburn I&A — MID Labs/Alcon MVS Systems — Microvit™ — OMS I/A — Cilco's I/A 2000™ and I/A Vitrophage™ 9000 — Site TXR™ — and many other I/A systems.

The biconvex optic design of these lenses provides a physiologic advantage and addresses one of the major issues confronting implanting surgeons: minimizing capsular opacification without increasing the probability of glare. The 94-KUV offers a 7.0-mm optic, and the P004-UV incorporates a 6.0-mm clear optic into this intraocular lens design.

Pharmaceuticals

Lederle Laboratories
3365 Tree Court Industrial Blvd.
St. Louis, MO 63122
Tel: (314) 225-5051



Neptazane methazolamide in 25-mg strength tablets is now available from Lederle Laboratories and Storz Ophthalmics in bottles of 100. The new strength tablets are designed to help ophthalmologists more easily titrate glaucoma therapy. Patients will no longer have to break Neptazane in 50-mg strength tablets during dose adjustments.

Bausch & Lomb Pharmaceuticals
11300 49th St. North
Clearwater, FL 34622-4807
Tel: (813) 572-4040

Bausch & Lomb Pharmaceuticals has introduced Bio-Cor 72 Collagen Corneal Shields, which provide patient comfort, protection, and lubrication for approximately 72 hours. Bio-Cor 72 Collagen Corneal Shields deliver extended relief from discomfort that results from postoperative, traumatic, and nontraumatic corneal conditions.

Manufactured from 100% porcine scleral collagen, the Bio-Cor 72 shield is clinically compatible with the collagen in the human eye. When hydrated by tears, it dissolves gradually to create a continuous protective layer.

Each shield is sterilized and packaged in a sterile pouch, marked with lot number and expiration date. Packaged two pouches per box, Bio-Cor 72 Collagen Corneal Shields are available in 12 packs, cases of 240, and in combination packs with other duration Bio-Cor 72 Collagen Corneal Shields.

Iolab Pharmaceuticals
500 Iolab Dr.
Claremont, CA 91711
Tel: (714) 624-2020

Iolab Pharmaceuticals, a division of Johnson & Johnson, now offers Miochol (acetylcholine chloride) in two new packages—Miochol System Pak and Miochol System Pak Plus IOCARE

BSS. Each Miochol System Pak includes Miochol, sterile 3-ml B-D syringe, sterile 0.2-μm DynaGard filter, and sterile IOCARE Steri-Tags. Miochol System Pak Plus IOCARE BSS includes all of the components in the Miochol System Pak plus two 15-ml bottles of IOCARE BSS.

Special for the Ophthalmologist!

Complete Zeiss Microsurgical Systems—OPMI® Operation Microscope, Stand, Accessories—configured for you, ready to use, priced right! All optics multi-coated.

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ZMS-104 SYSTEM

MICROSCOPE BODY 19-FR with magnification changer in 5 steps, built-in FR coaxial illumination system with retinal protection device, receptacle for insertable filter sliders, and dovetail for illumination accessories
Objective f = 175mm
Inclined binocular tube f = 170
2 Screw-mount, Wide-field, High-eyepoint eyepieces 10 × /22B
Fiber Optic Illuminator
STANDARD-0 STAND with column 1880mm, sliding microscope carrier arm, motor drive head and foot switch.

ZMS-101 SYSTEM

MICROSCOPE BODY 6S-FR with motorized 1:4 zoom system w/manual override, built-in FR coaxial illumination system with retinal protection device, receptacle for insertable filter sliders, and dovetail for illumination accessories
Objective f = 175mm
Inclinable 0-60° Binocular Tube f = 170
2 Screw-mount, Wide-field, High-eyepoint eyepieces 10 × /22B
Motorized X-Y Adjustment Coupling 2 with Automatic Recentering
UNIVERSAL S-3-B FLOORSTAND with 14-Function Foot Control Panel
DUO Fiber Optic Illumination System
Horizontal Arm for suspension of microscope

ZMS-102 SYSTEM

MICROSCOPE BODY 6C-FR
UNIVERSAL S-3-B FLOORSTAND

ZMS-103 SYSTEM

MICROSCOPE BODY 6S-FR with motorized 1:4 zoom system w/manual override, built-in FR coaxial illumination system with retinal protection device, receptacle for insertable filter sliders, and dovetail for illumination accessories
Insertable filter slider with UV filter GG475
Objective f = 175mm
Inclined binocular tube f = 170
2 Screw-mount, Wide-field, High-eyepoint eyepieces 10 × /22B
Fiber Optic Illuminator with fiber optic light guide
STANDARD-B STAND with column 1880mm, sliding microscope carrier arm and 12-Function Foot Control Panel

For the full story on these systems, contact your Zeiss dealer. For the name of your nearest dealer, call (800) 522-5204. In New York, call (914) 681-7768.

Carl Zeiss, Inc.
One Zeiss Drive
Thornwood, NY 10594
914 • 747 • 1800

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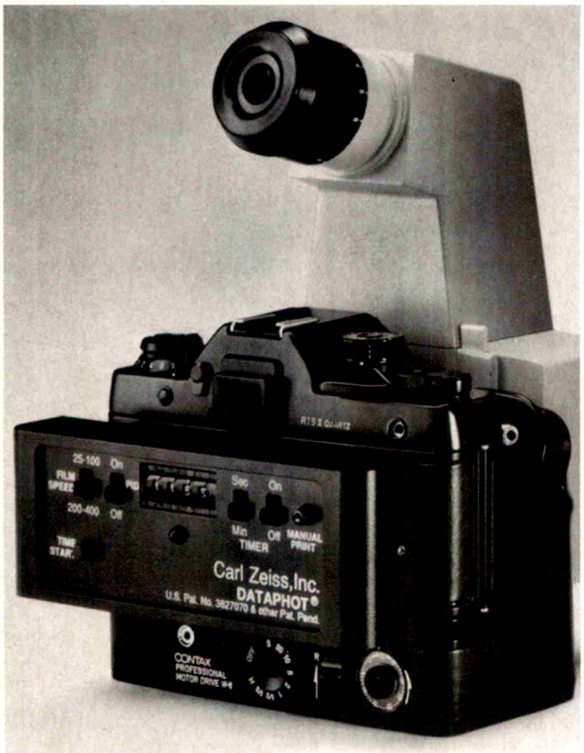
West Germany

Diagnostic Equipment

Carl Zeiss, Inc.
One Zeiss Dr.
Thornwood, NJ 10594
Tel: (914) 747-1800

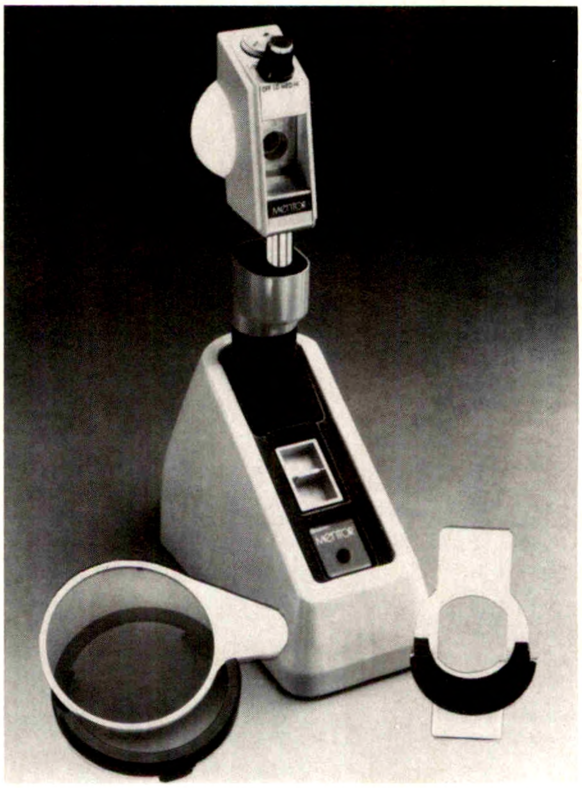


Carl Zeiss, Inc., is now offering DATAPHOT II, which imprints both patient identification numbers and photographic time intervals during fluorescein angiography. The DATAPHOT II attaches to the Zeiss FF-4 and FK-30 fundus cameras, 75 SL/P slit lamp, and 40 SL photo slit lamp. The device may also be used with selected 35-mm cameras, including the Contax RTS2 with professional motor drive and the Nikon F3 with MD4 motor drive.

For ease of operation, DATAPHOT II is triggered through the fundus camera or photo slit-lamp switch and is automatically synchronized with the 35-mm camera shutter. The device allows sequenced time signatures as fast as one-tenth per second and patient identification numbers of up to four digits. An ergonomically located starter button ensures easy startup without having to locate the switch visually. Precise recording continues up to 1,000 seconds before resetting.

If no data imprinting is required, both patient identification numbers and timing functions can be independently switched off. DATAPHOT II can accommodate film speeds ranging from ASA 25 to 100, and 200 to 400.

Mentor O & O, Inc.
3000 Longwater Dr.
Norwell, MA 02061
Tel: (617) 871-6950

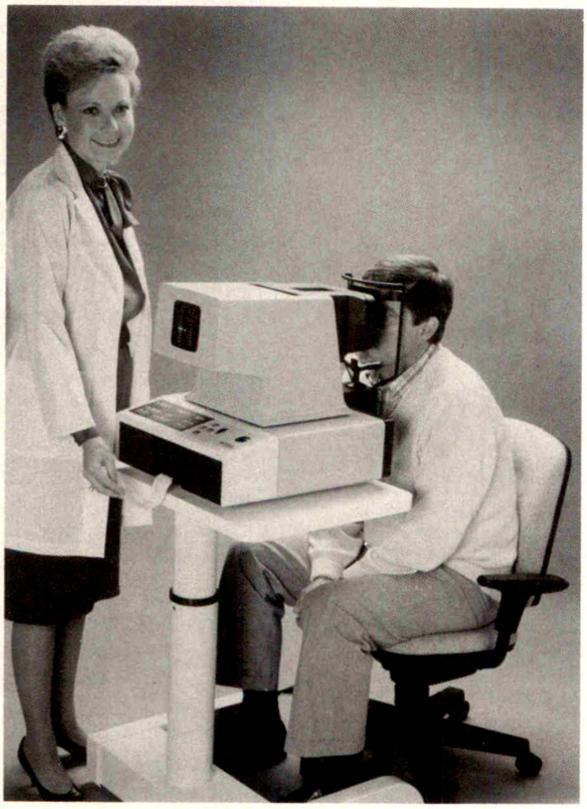


Mentor O & O, Inc., has developed three new accessories for its BAT brightness acuity tester. The tinted lens holder (Product No. 22-4517) can be used to evaluate tinted lenses under different glare conditions to determine if any special tints can help reduce mild functional vision complaints. Any tinted lens, 65 mm in diameter, will fit the clip-on holder and the lens rings.

The tinted lens ring holder (Product No. 22-4518) is designed to be used with the tinted lens holder and contains ten tinted lens rings. This set facilitates the use of tinted lenses during patient testing and also helps to keep the lenses clean.

The trial lens holder (Product No. 22-4516) facilitates the use of trial lenses, if required, to assure testing is conducted with the patient's best visual acuity.

Allergan Humphrey
3081 Teagarden St.
San Leandro, CA 94577
Tel: (800) 227-1508 (National)
(800) 826-6566 (California)



Allergan Humphrey has introduced automatic refractor Models 550, 560, and 570. The new models feature automatic, operator-independent alignment. The instruments are automatically positioned at the proper vertex for each patient. A preprogrammed sequence mode automatically aligns, measures both eyes, prints, and clears at the touch of a control for faster, easier objective refractions.

Each of the new Humphrey automatic refractors will also automatically calculate and print the patient's pupillary distance. Models 560 and 570 include glare testing and various subjective features. Model 550 is an objective-only refractor.

Contact Lens Supplies

Bausch & Lomb
Personal Products Division
Rochester, NY 14692-0450
Tel: (716) 338-6000

Bausch & Lomb has introduced a new buffered formula HYPO-CLEAR sterile saline spray for soft contact lens wearers that helps ensure patient comfort and encourage patient compliance. The 100% preservative-free aerosol spray now has a borate-buffered formulation. This buffer system more closely matches the pH of the human eye. A 360-degree nozzle that will spray from any angle has also been added. In addition to patient convenience, this feature reduces the potential for unused saline remaining in the aerosol can.

The improved saline spray is available in some Bausch & Lomb thermal care kits in a 4-fl oz size and at retail stores in 8- and 12-fl oz sizes.

OPHTHALMOLOGIST

Navajo Nation Health Foundation in Ganado, Arizona is seeking an ophthalmologist to continue and build the first non-federal practice on the Reservation. Join staff of nine primary-care physicians providing services to Native Americans in the high desert country of the Colorado Plateau. Send C.V. to Cathy Carpenter, M.D., Medical Director, Sage Memorial Hospital, Box 457, Ganado, Arizona 86505.

NORTHERN CALIFORNIA: General ophthalmologist or subspecialist to join 3-man group in well equipped San Jose office. Reply to: Chief of Ophthalmology, The Permanente Medical Group, Inc., 270 International Circle, San Jose, California 95119-1197.

MEDICAL RETINA/LASER

Vitreoretinal group practice in the Southeast has a full-time position for a physician to provide full medical retina/laser/retinal diagnostic services for the main office of a 7-physician retina subspecialty group active in high quality tertiary referral care, research, publication, and resident education. Will provide training if necessary. Salary negotiable. Send complete CV to Box 069 AJO.

FACULTY POSITION

Available for ophthalmologist with a subspecialty interest in vitreoretinal surgery to participate in clinical consultations, research and teaching. M.D. degree and completion of approved U.S. residency. With one or two years of fellowship training. Board eligible or certified. Florida license required. Affirmative action/equal opportunity employer. Contact: Dr. Edward W. D. Norton, M.D., Bascom Palmer Eye Institute, P. O. Box 016880, Miami, FL 33101.

ASSOCIATE: Busy two-man ophthalmology group with excellent clinical and surgical practice, seeks third associate to do cornea and general ophthalmology. Will consider other subspecialties. Location: Ann Arbor, MI. Competitive salary and benefits package. Start July 1989. Reply Box 043 AJO.

SOUTHWEST MICHIGAN

Beautiful historic community in southwest Michigan is actively seeking a BE/BC Ophthalmologist to complement an active, progressive medical staff. Outstanding growth potential with extensive practice support guaranteed. A competitive compensation and benefit package will be tailored to the candidates needs. Send C.V. or contact: Linda M. Richardson, Bronson Management Services Corporation, 150 East Crosstown Parkway, Suite 215, Kalamazoo, Michigan 49001, (616) 344-6444.

SEEKING MEDICAL OPHTHALMOLOGIST: with experience in glaucoma, pediatric and/or oculoplastic for well-established West Coast Florida eye clinic. Generous compensation package. Forward recent photograph and C.V. to P.O. Box 40457, St. Petersburg, Florida 33743-0457.

OHIO RETINA OR PEDIATRICS: Fellowship-trained physician to complement busy cataract surgeon. We have the latest equipment and a talented staff. Outstanding opportunity. Salary with incentives, fringe benefits and malpractice insurance. May work part time, if desired. Reply to Box 070 AJO.

PEDIATRICS

Busy ophthalmic group practice with rapidly expanding surgical patient load seeks additional ophthalmologist with subspecialty fellowship or interest in pediatric ophthalmology. State-of-the-art Clinical Eye Center with approved freestanding outpatient ophthalmic surgical facilty. Beautiful and convenient Mid-Atlantic location within short driving distance to Washington, Baltimore, and Philadephia. Reply to Box 071 AJO.

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We are a 46 physician multi-specialty Group seeking a Board Certified/Eligible General Ophthalmologist. The Eye Department consists of two Ophthalmologists and optometric support. We offer a competitive salary first year with production incentive, partnership thereafter. For additional information, please send CV to:

Warren J. Boyer, Jr., M.D.
Marysville Medical Group
800 Third Street
Marysville, California
95901-5889

GLAUCOMA

Ophthalmologist with subspecialty training in glaucoma is sought for full-time position in University Department of Ophthalmology, academic rank commensurate with credentials. Must have completed an approved eye residency program, appropriate fellowship training and be Board certified or eligible. Duties include teaching residents and medical students, patient care and research. Send curriculum vitae, publications list and the names and addresses of 3 references to:

JAMES P. MC CULLEY, M.D.
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FELLOWSHIPS

CORNEA FELLOWSHIP

One year Fellowship in Cornea and External Diseases available 7/1/89. High volume transplant and refractive surgery practice with opportunity for clinical research. Located in residential area of northern New Jersey, 20 miles west of Manhattan. Address C.V. and inquiries to Theodore Perl, M.D., Corneal Associates of New Jersey, 101 Old Short Hills Road, Suite 410, West Orange, New Jersey 07052 (201) 736-1313.

NEURO—OPHTHALMOLOGY FELLOWSHIP
DEPARTMENT OF OPHTHALMOLOGY
UNIVERSITY OF MIAMI

A twelve month post-graduate fellowship in clinical neuro-ophthalmology is available beginning July 1989 through June 1990 for ophthalmologist or neurologist interested in academic career. Affirmative action equal opportunity employer. Contact: Joel S. Glaser, M.D., Bascom Palmer Eye Institute, P.O. Box 016880, Miami, Florida 33101.

FELLOWSHIP: Corneal external disease fellowship available July 1, 1990. Clinical and animal research required. Contact: Richard A. Eiferman, M.D., University of Louisville, 301 E. Muhammad Ali Blvd., Louisville, KY 40202.

POSITIONS WANTED

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Devron H. Char, M.D., Kim Huhta, B.S., and Frederic Waldman, M.D.

We histologically studied uveal melanomas treated with surgery only (enucleation or ciliochoroidectomy), low-dose (20 Gy) preenucleation radiation followed by enucleation, or enucleated melanomas after high-dose (50 to 80 Gy) charged-particle beam therapy. There was significantly less bromodeoxyuridine uptake in irradiated vs nonradiated melanomas ($P < .0001$). Similarly, tissue culture growth of irradiated tumors was significantly less ($P < .007$). These data demonstrate destruction of reproductive integrity of helium ion-irradiated melanomas. The incorporation of bromodeoxyuridine and fine needle aspiration biopsy techniques may be useful in the delineation of successfully irradiated tumors from tumors with apparent growth secondary to radiation vasculopathy.

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Contralateral Trochlear Nerve Paresis and Ipsilateral Horner's Syndrome

John Guy, M.D., Arthur L. Day, M.D., J. Parker Mickle, M.D., and Norman J. Schatz, M.D.

Two patients had paresis of the trochlear nerve contralateral to the site of lesions in the brainstem. Both patients had ipsilateral blepharoptosis and miosis suggesting oculosympathetic paresis from involvement of the descending sympathetic tract, adjacent to the fourth cranial nerve nucleus and its fascicles, in the caudal mesencephalon. Cerebral angiography documented an arteriovenous malformation of the brainstem in Case 1. Magnetic resonance imaging disclosed a lesion of high signal intensity on T_2-weighted images involving the dorsal mesencephalon in Case 2. Involvement of the superior cerebellar peduncle produced ipsilateral dysmetria and ataxia. Lesions involving the fourth cranial nerve nucleus or its fascicles, before decussation in the superior medullary velum, and adjacent sympathetic fibers may produce an ipsilateral Horner's syndrome and contralateral superior oblique muscle paresis.

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Thomas M. Aaberg, M.D.

Lyme disease is characterized by three clinical stages. Ophthalmologic abnormalities, which have been documented during each of the three stages, manifest as transient conjunctivitis, keratitis, optic disk edema, retinal edema, retinal vasculitis, exudative retinal detachment, iridocyclitis, and paresis of the third and sixth cranial nerves. The diagnosis of Lyme disease is confirmed by a combination of clinical signs and results of serologic testing. Fortunately, the response to therapy is usual and satisfactory when the disease is discovered in the early stages.

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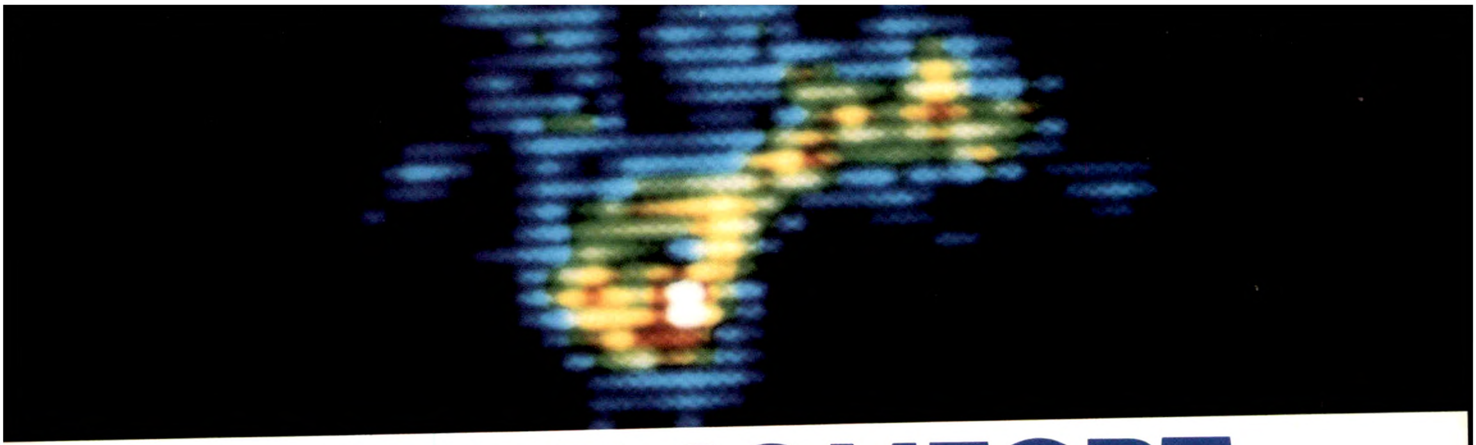

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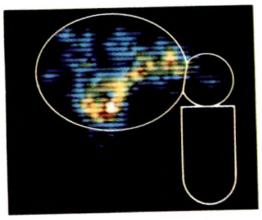

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1. Multi-Center Study, Comfort Evaluation of HypoTears vs Tears Naturale. Abelson, MB. Eye Research Institute, Boston, Massachusetts, 1987.
2. Holly and Esquivel. Colloid osmotic pressure of artificial tears. Prepublication, 1985.
3. Applications of Lacrimal Scintigraphy to the Development of Ophthalmic Formulations. Olejnik O, Wilson CG, Fitzgerald P. Monograph. Queens Medical Centre, Nottingham, England, 1987.

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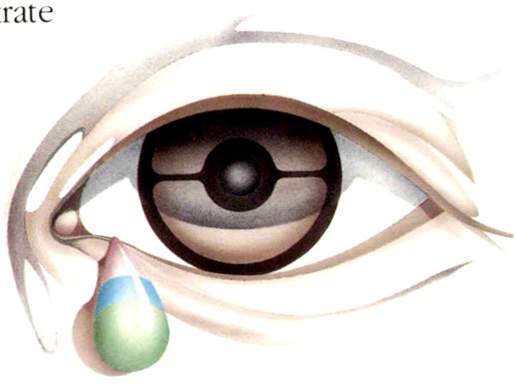

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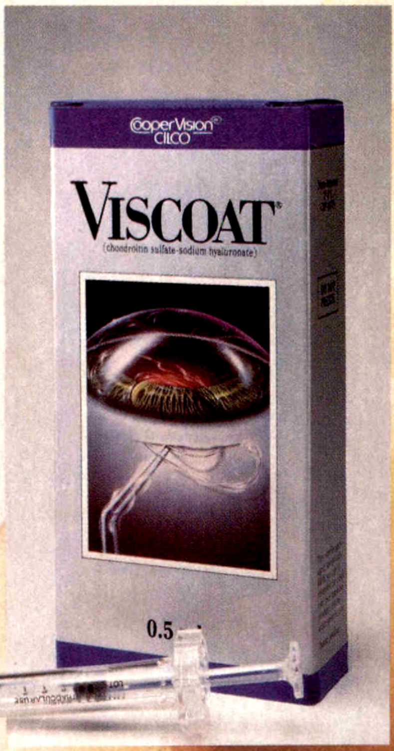

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Glasser D: Protective effects of viscous solutions during phacoemulsification and lens implantation. Presented at the ASCRS Meeting, Century City, CA, March 29, 1988.
Stein RM, Laibson PR: Comparison of chondroitin sulfate to McCarey-Kaufman medium for corneal storage. *Am J Ophthalmol* 1987;104: 490-493.

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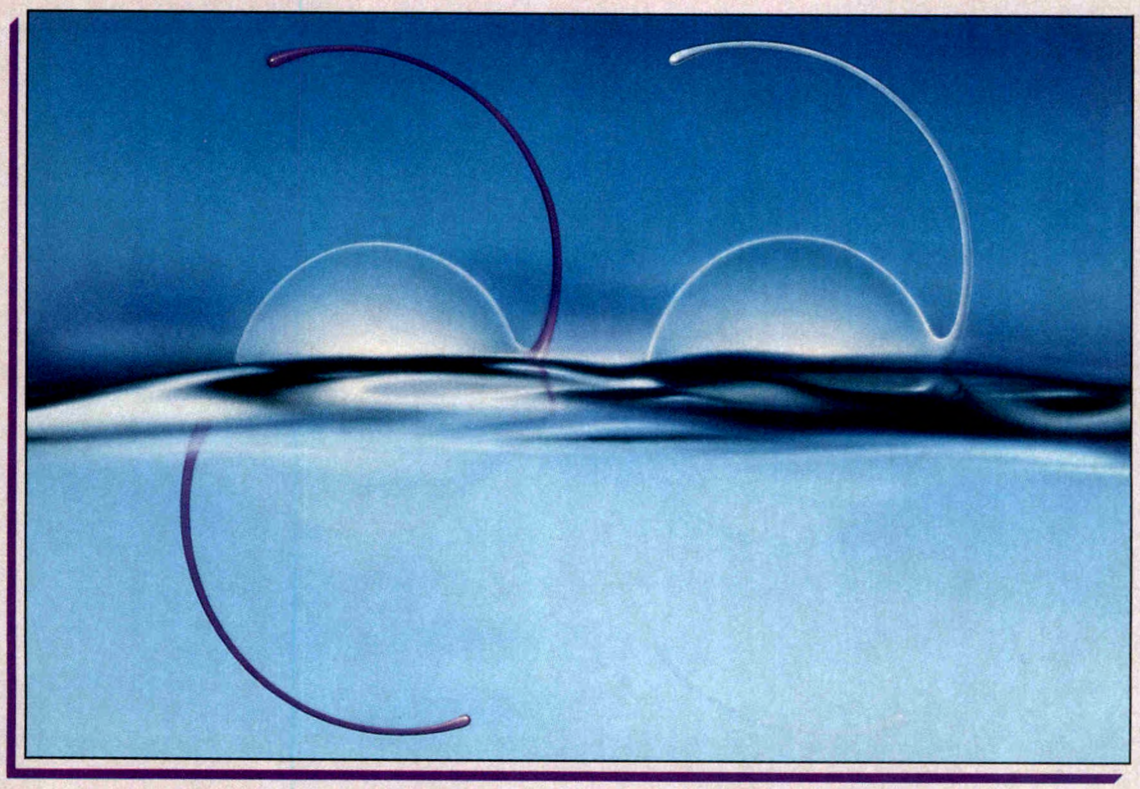

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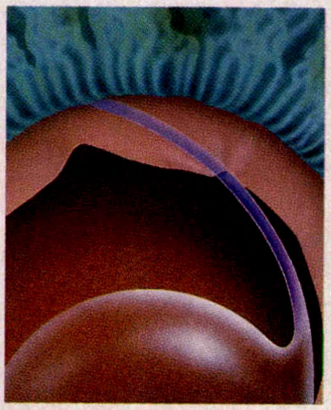

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CONTRAINDICATIONS: At the present time, there are no known contraindications to the use of VISCOAT® when used as recommended.

PRECAUTIONS: Precautions are limited to those normally associated with the surgical procedure being performed. Although sodium hyaluronate and sodium chondroitin sulfate are highly purified biological polymers, the physician should be aware of the potential allergic risks inherent in the use of any biological material.

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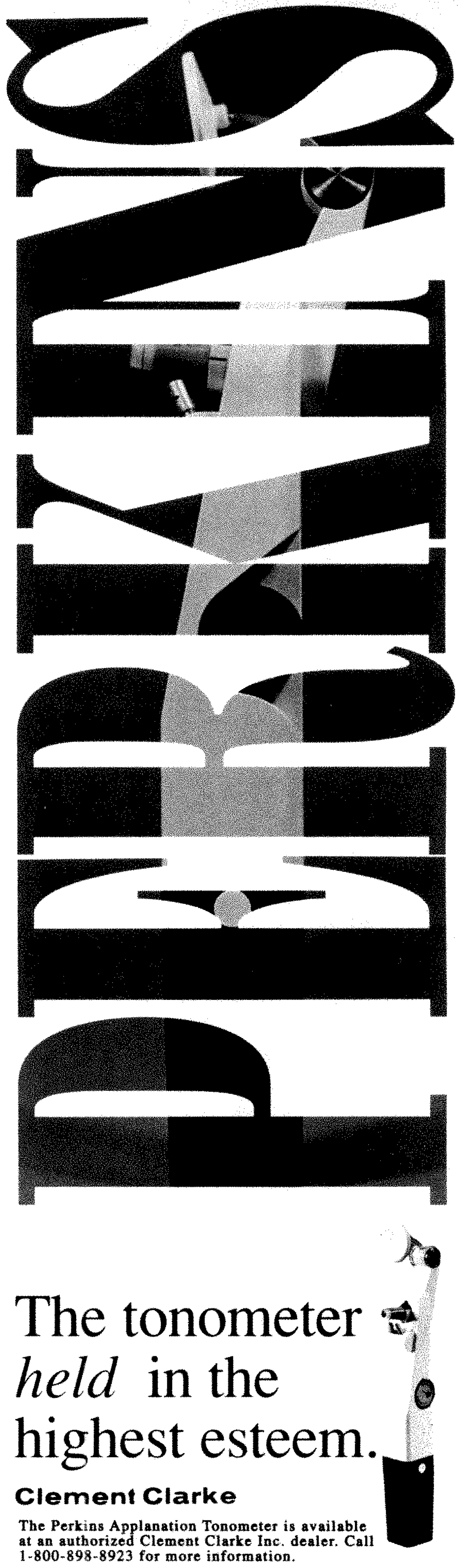

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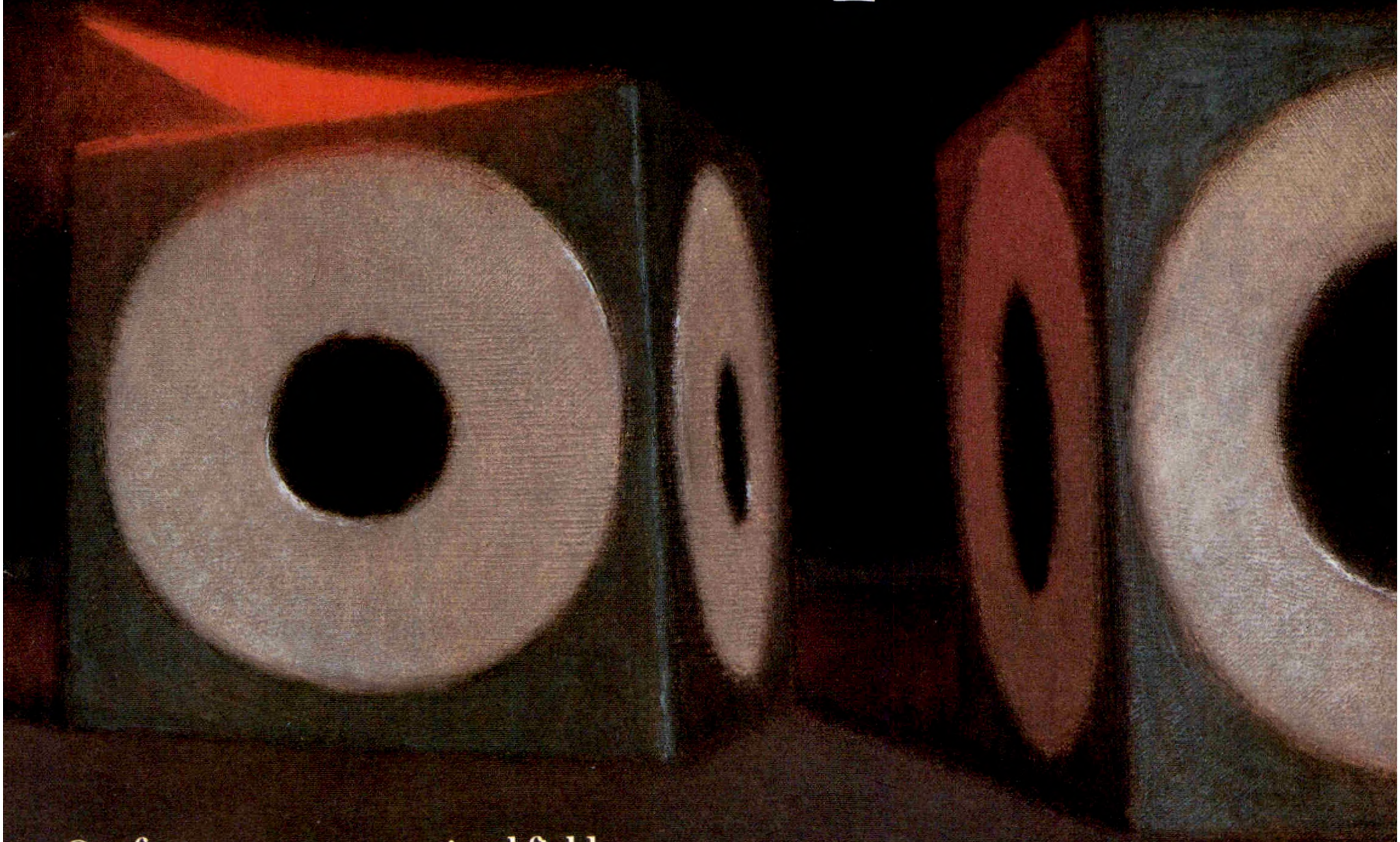

Ocufen preserves your visual field.

Since Ocufen helps keep the pupil larger, you have a better view of the posterior chamber. So you can safely and thoroughly remove the lens nucleus and cortical material. . .effectively position and insert the IOL. . .and reduce the risk of ocular trauma and complications. Ocufen gives you a new measure of control over the unexpected.

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But would I rather see a larger pupil? Of course.
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Please see brief summary of prescribing information on the next page.

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(flurbiprofen sodium) 0.03%
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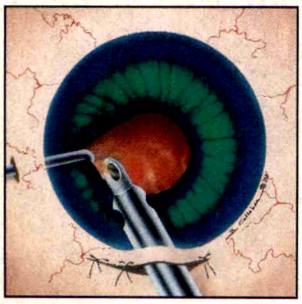
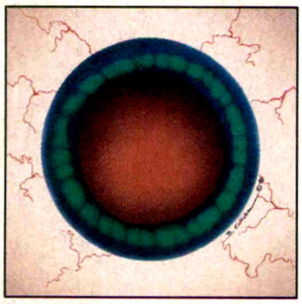


Miosis can pose difficulties in locating and removing residual cortical material.

IOL insertion through a small pupil may prove difficult.

Repeated manipulation of the iris may occur during phacoemulsification, when miosis has developed.

With Ocufen



Residual cortical material may be easily located and removed.

IOL insertion and positioning within the capsular bag is facilitated.

Potential risk of iris insult and other ocular trauma is decreased.

INDICATIONS AND USAGE

Ocufen is indicated for the inhibition of intraoperative miosis.

CONTRAINDICATIONS

Ocufen is contraindicated in epithelial herpes simplex keratitis (dendritic keratitis) and in individuals who are hypersensitive to any components of the medication.

WARNINGS

There exists the potential for cross-sensitivity to acetylsalicylic acid and other nonsteroidal anti-inflammatory drugs. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

PRECAUTIONS

General: Patients with histories of herpes simplex keratitis should be monitored closely. Ocufen is contraindicated in patients with active herpes simplex keratitis.

Wound healing may be delayed with the use of Ocufen.

Drug interactions: Interaction of Ocufen® (flurbiprofen sodium) 0.03% Liquifilm® sterile ophthalmic solution with other topical ophthalmic medications has not been fully investigated.

Although clinical studies with acetylcholine chloride and animal studies with acetylcholine chloride or carbachol revealed no interference, and there is no known pharm cological basis for an interaction, there have been reports that acetylcholine chloride and carbachol have been ineffective when used in patients treated with Ocufen.

Carcinogenesis, mutagenesis, impairment of fertility: Long-term studies in mice and/or rats have shown no evidence of carcinogenicity or impairment of fertility with flurbiprofen.

Long-term mutagenicity studies in animals have not been performed.

Pregnancy:

Pregnancy category C. Flurbiprofen has been shown to be embryocidal, delay parturition, prolong gestation, reduce weight, and/or slightly retard growth of fetuses when given to rats in daily oral doses of 0.4 mg/kg (approximately 185 times the hum daily topical dose) and above. There are no adequate and well-controlled studies in pregnant women. Ocufen should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from flurbiprofen sodium, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

The most frequent adverse reactions reported with the use of Ocufen are transient burning and stinging upon instillation and other minor symptoms of ocular irritation.

It is known that some systemic absorption does occur with ocularly applied drugs, an that nonsteroidal anti-inflammatory drugs have been shown to increase bleeding tim by interference with thrombocyte aggregation. There have been reports that ocularly applied Ocufen may cause an increased bleeding tendency of ocular tissues in conjunction with surgery. It is recommended that Ocufen be used with caution in surgic patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

Ocufen® helps you control the unexpected

(flurbiprofen sodium) 0.03%
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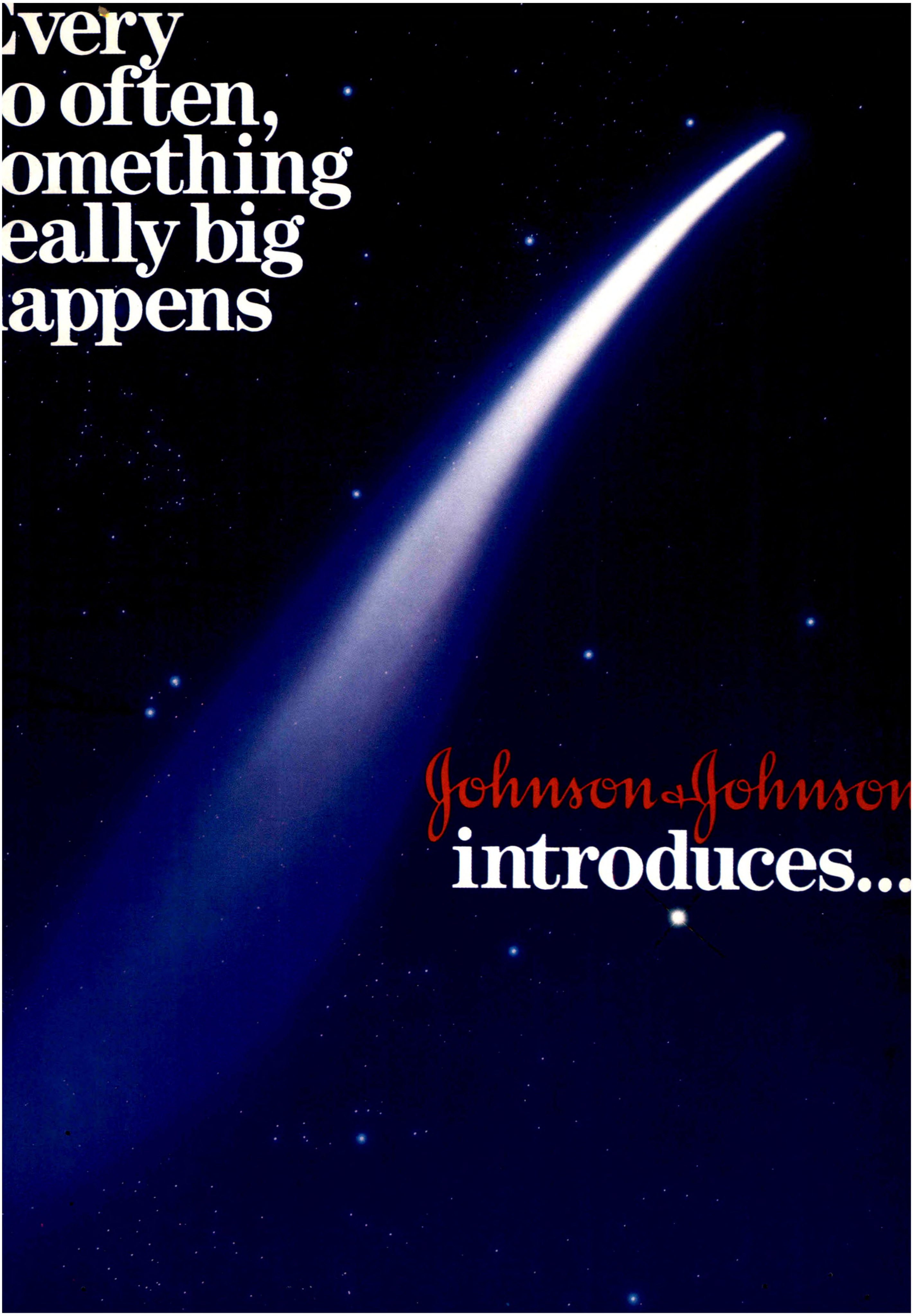
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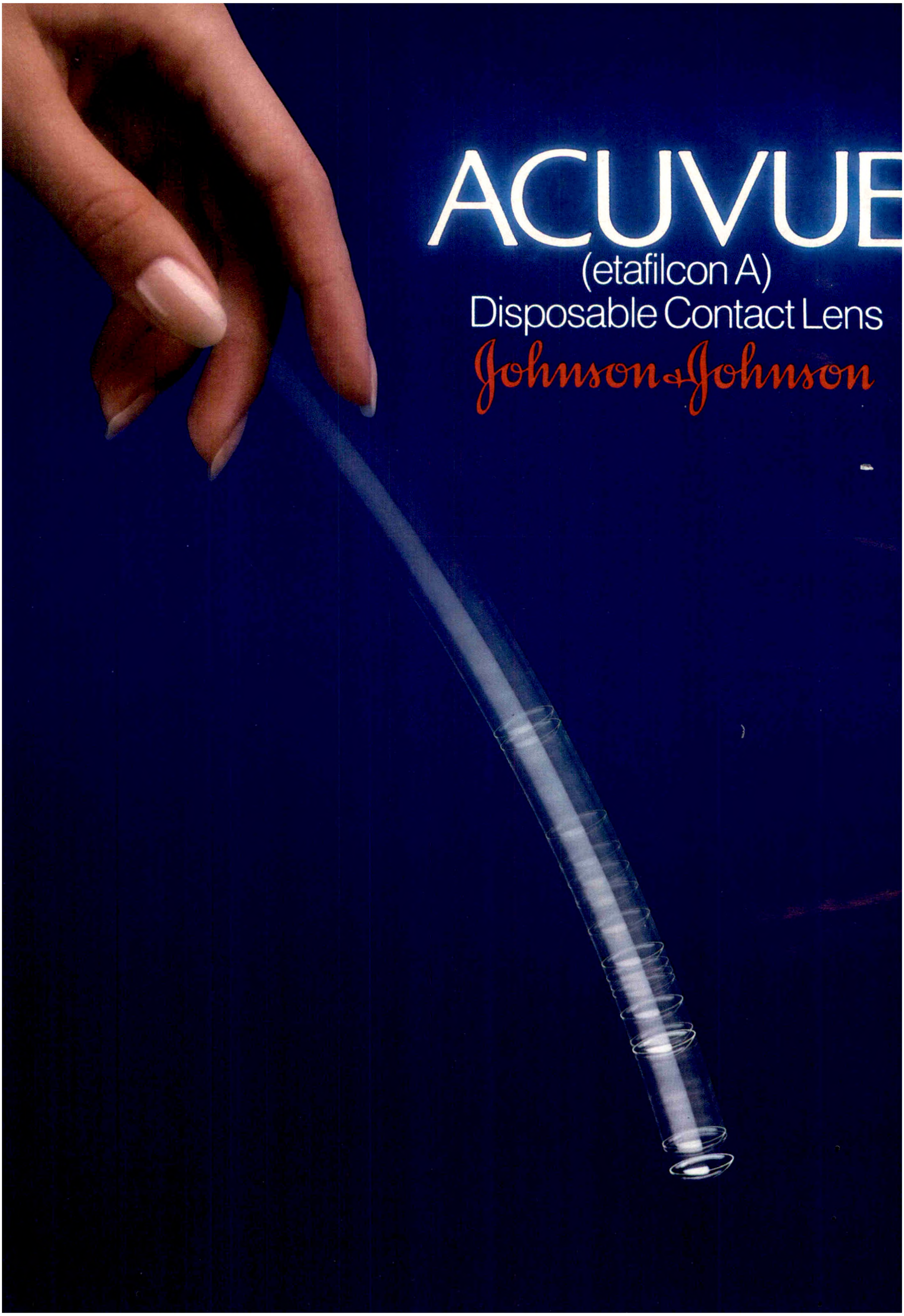
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ears of research and development have made ossible the production of ACUVUE lenses by a nique new *Stabilized Soft Molding* process, whereby ACUVUE is produced entirely in the soft, vet state. This multipatented process provides n entirely new standard of precision, eliminating he hydration distortions common to traditional ard state manufacturing. The result is a totally ew, high quality lens that is virtually 100% epeatable, offering excellent vision and comfort, nd making disposability a practical reality.

Superior visual acuity

When eye care practitioners compared ACUVUE to conventional, reusable contact lenses, 71% rated ACUVUE superior in visual acuity.[1] And 69% of patients surveyed agreed that ACUVUE provided crisper, sharper vision than their previous form of vision correction.[2]

Superior comfort

In a recent survey of practitioners, 85% agreed that their patients reported comfort as better or superior to conventional, reusable contact lenses.[1] Patient response was especially favorable: no less than 77% reported ACUVUE to be more comfortable week after week.[2]

Most importantly, ACUVUE provides this outstanding performance in visual acuity, comfort, and reliability continually, lens after lens after lens!

Now the better choice in vision correction is here!

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(etafilcon A)
Disposable Contact Lens
Johnson & Johnson

Superior eye health through the simplest system of lens wear

Because ACUVUE is worn for about a week, then thrown away, long term lens deposit buildup is eliminated...and so are the eye irritations and risks to corneal health associated with long term buildup. No reusable contact lens can offer this safety benefit because, even with proper cleaning, protein and other deposits continually build up. ACUVUE encourages patient compliance by requiring no cleaning or disinfecting: patients simply dispose of those potential problems when they dispose of the lens.

Scanning electron photo-micrographs demonstrate the ACUVUE advantage:

An extended wear lens after 1 month with patient care: Deposit buildup evident*

A daily wear lens after 1 month with patient care: Deposit buildup evident*

ACUVUE Disposable Contact Lens after 1 week: Minimal deposit buildup

And since cleaning and disinfecting solutions are eliminated with the disposable regimen, patients using ACUVUE are not at risk for allergic reactions associated with solutions. Here's what practitioners reported when asked about the ACUVUE health advantage: 95% agreed that disposable wear was safer and healthier than conventional, reusable contact lenses![1]

The most convenient regimen for patient compliance

ACUVUE makes patient compliance as simple as possible: patients simply dispose of the lenses aft use. That means there is no care regimen for the to follow. No solutions to buy, use, or carry. No tin expended for maintenance. No inconvenience. Nothing could be simpler than the ACUVUE easy to-follow wear schedule. In fact, 98% of practitione surveyed found that patient compliance with ACUVUE met or exceeded their expectations![1]

*Representative of over 50 lenses obtained by an independent practitioner from patients who reported their compliance regimens.

Now the better choice in vision correction is here!

An outstanding practice building opportunity for you

Here's what ACUVUE can provide specifically for your practice: increased profits per patient; greater patient retention because you control the supply of lenses; ongoing revenue, plus the potential to substantially increase your patient base...including the possibility of recapturing contact lens dropouts.

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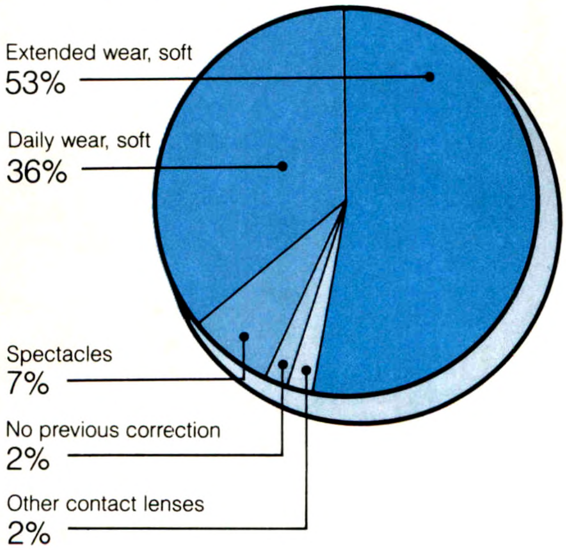

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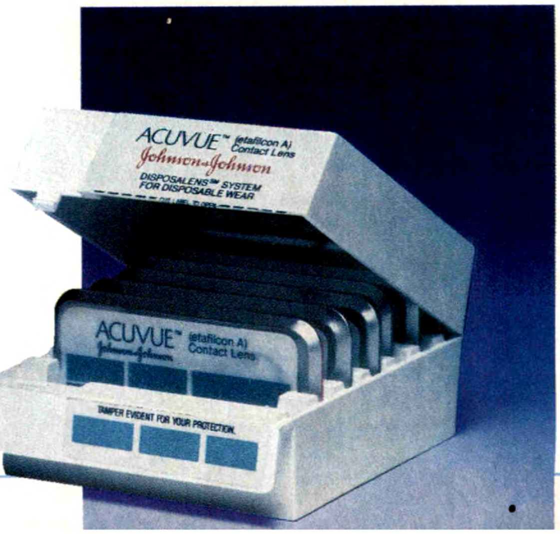

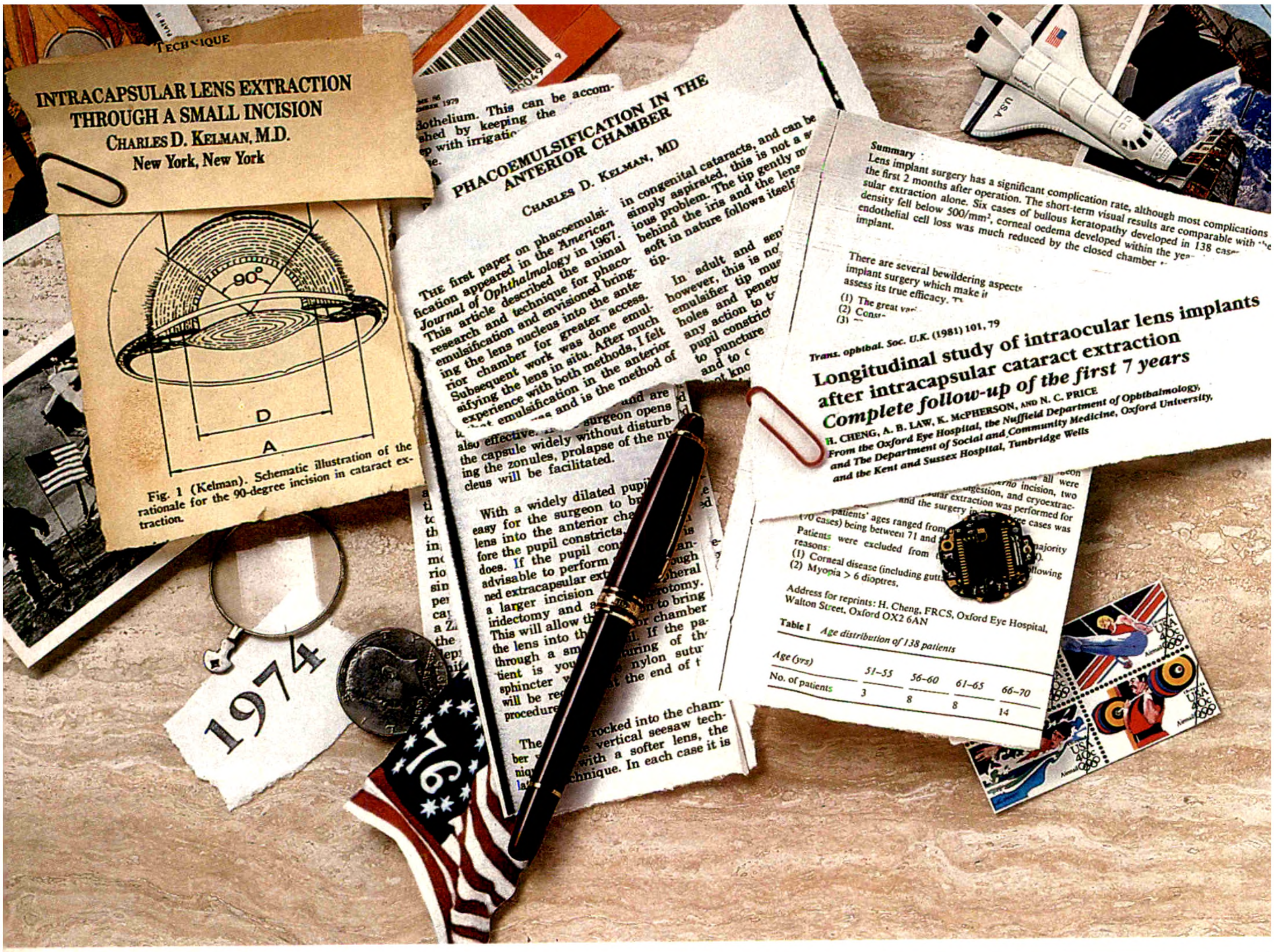
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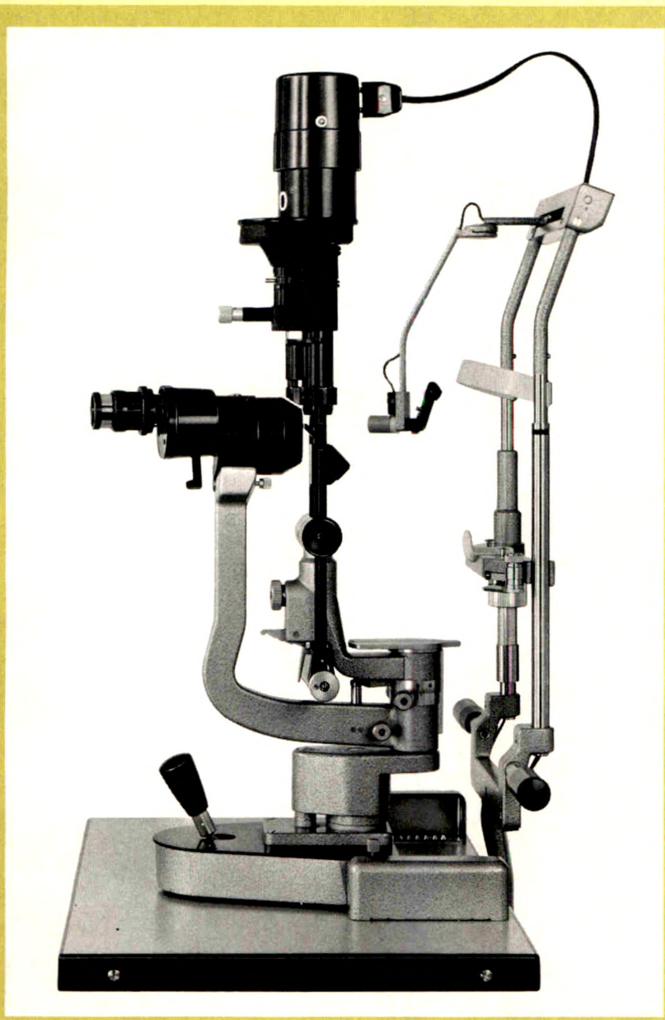

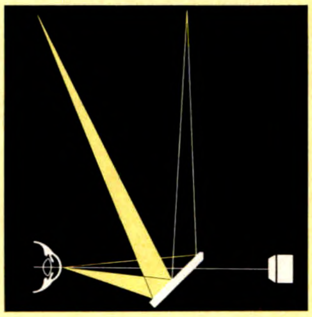

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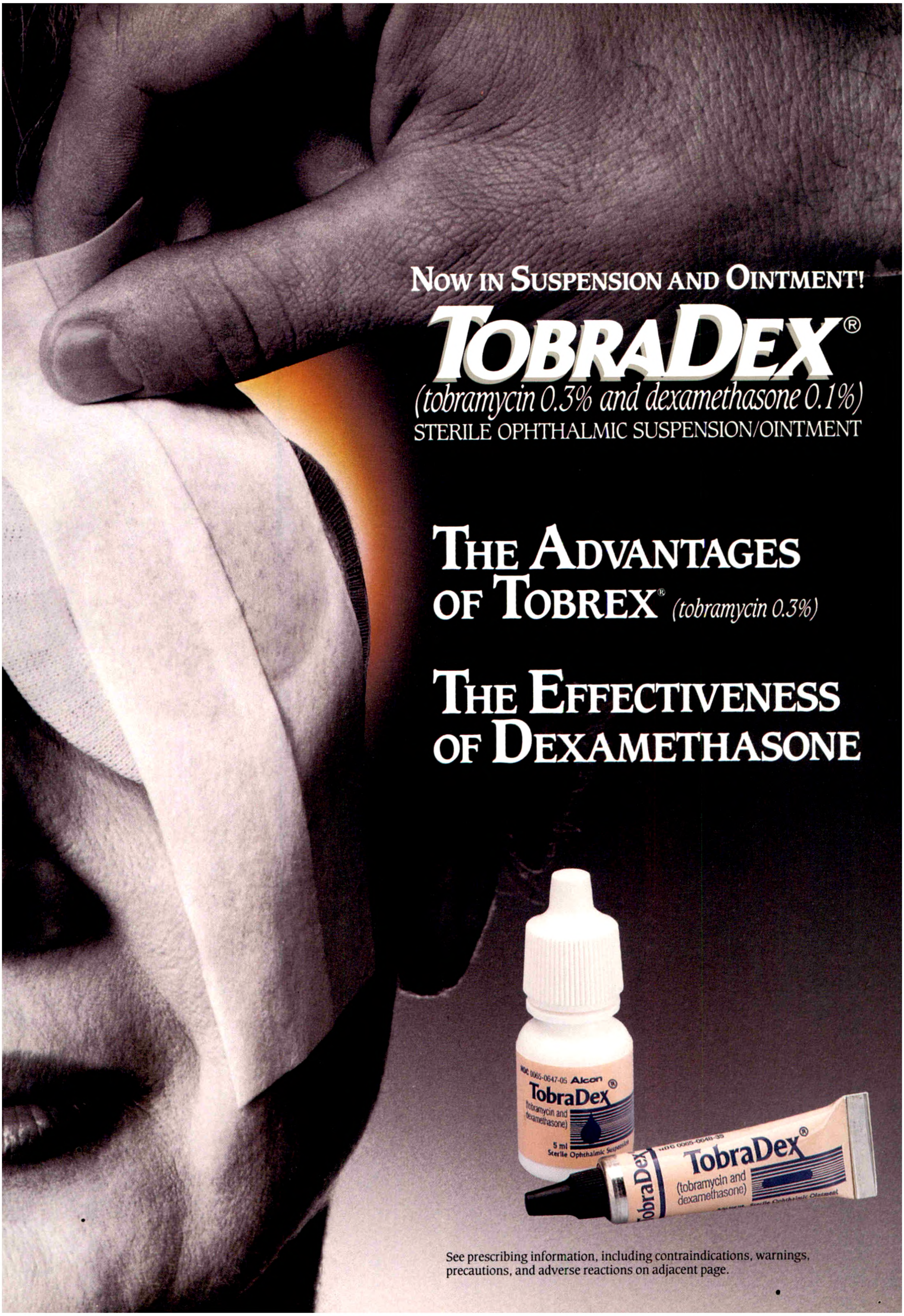
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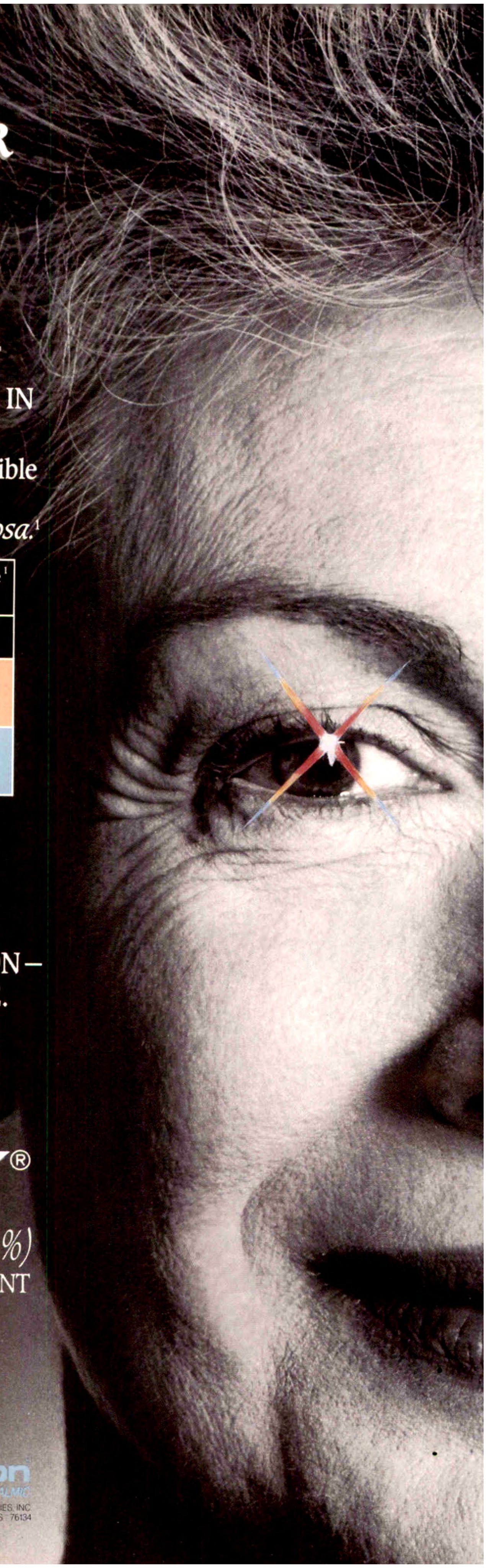

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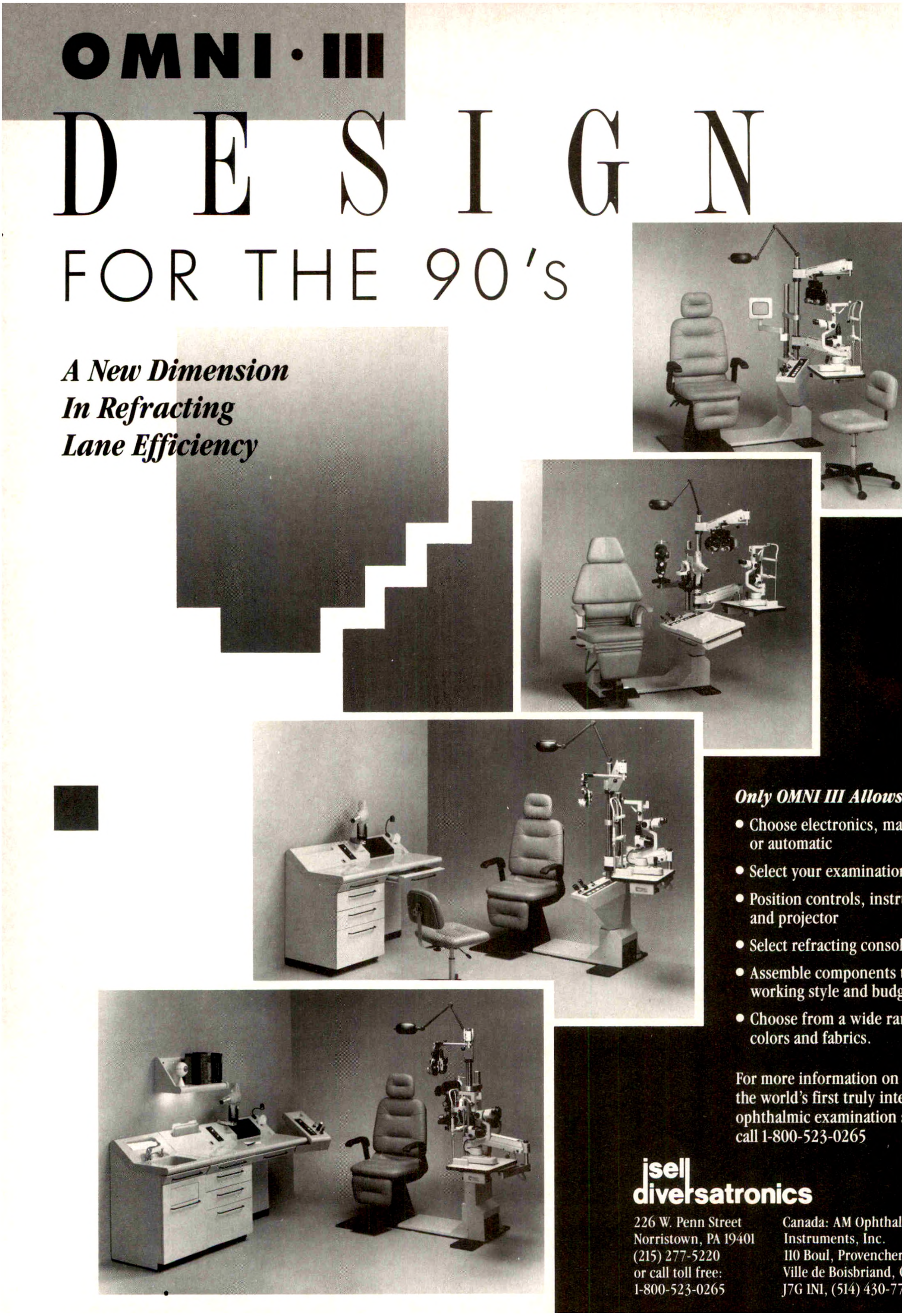

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Glaucoma &

The Age of Risk

The fact that almost 70% of glaucoma patients are over 60 years of age[1] has important implications regarding their overall health status.

Even in younger patients, the local arteriosclerosis characteristic of glaucoma is frequently accompanied by clinical evidence of similar damage to cerebral, cardiac and renal vessels, or to the entire circulatory system.[1] The more typical older patient runs an independent risk of age-related changes in cardiopulmonary and metabolic function.

In fact, prevalence studies indicate that more than half of all glaucoma patients have concurrent cardiovascular disease,[1] and run over twice the risk of the general population of developing diabetes.[2]

DISEASE STATE	INCIDENCE COEXISTENCE WITH GLAUCOMA[1]
Hypertension	**54.5%**
Arteriosclerosis	**58.8%**
Diabetes	**15.9%**

Beyond Normotension

Such statistics mandate that your considerations in selection of a therapeutic regimen for all glaucoma patients go well beyond lowering IOP to the normotensive range.

Ophthalmic beta blockers are clearly today's drug of choice for management of elevated IOP, but the record of nonselective agents raises serious questions regarding their safety in the elderly patient. Side effects associated with orally administered nonselective beta blockers have been seen with those employed ophthalmologically.[3] In fact, all beta blockers are contraindicated in patients with sinus bradycardia, greater than a first-degree atrioventricular block, cardiogenic shock or overt cardiac failure.

Systemic effects of nonselective beta blockers[3-5]

CARDIOVASCULAR	PULMONARY
Arrhythmia	Asthma
Bradycardia	Bronchial constriction
Cerebrovascular accident	Bronchospasm
Hypotension	**DRUG INTERACTIONS**
Raynaud's phenomenon	Oral beta blockers
Syncope	Calcium antagonists
Palpitation	Reserpine
Congestive heart failure	Digitalis
	Bronchodilators
	Insulin

Systemic Spillover

The mechanisms for this "systemic spillover" of ophthalmic beta blocker effects are both pharmacologic and pharmacokinetic.

From a pharmacokinetic standpoint, it's important to note that all eyedrops drain through the nasolacrimal system rapidly. An estimated 80% of the drug may be absorbed through the nasal mucosa directly into the bloodstream, thus reaching target organs without first being metabolized in the liver (first-pass effect).[3]

Pharmacologically, nonselective agents block both beta-1and beta-2 receptors. Thus, the potential for pulmonary and metabolic as well as cardiovascular side effects is significant.[3]

The Promise of Oculoselectivity

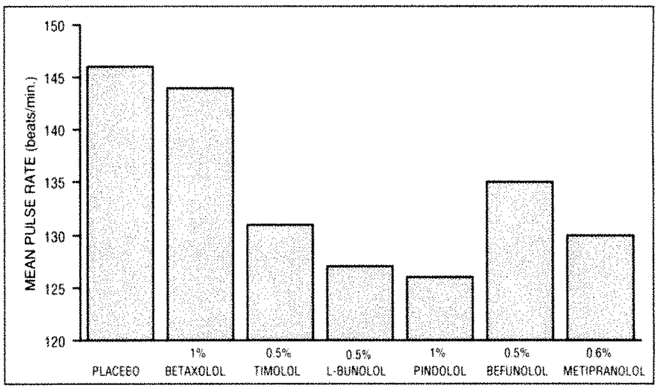
A new generation of oculoselective beta blocking agents offers hope of overcoming most of the systemic spillover associated with nonselective agents.

The beta-1 selectivity of these agents strongly diminishes their effect on organs containing beta-2 receptors and, therefore, the risk of bronchial constriction, peripheral vascular constriction and altered glucose metabolism.[4]

The pharmacokinetic profile of the oculoselective agent is similarly unique. It exhibits a high degree of lipid-solubility which permits penetration of the corneal surface in order to reach the desired site of action.[6]

Lipid-solubility, furthermore, accounts for a high volume of distribution throughout extra- and intracellular spaces, so that beta-blocking activity remains low throughout the body. In addition, more drug is bound to plasma protein, and less free drug is available to interact with receptors throughout the body. Such is not the case with nonselective beta blockers which exhibit significant plasma activity even after ophthalmic administration.[6]

Numerous clinical studies support the lack of systemic spillover with oculoselective beta blockers. These agents demonstrate little effect on cardiopulmonary function, and would not be expected to interfere with concomitant medications including calcium channel blockers, diuretics, digitalis, oral beta blockers, bronchodilators or insulin therapy.[7-10]



Relative effects of selective and various nonselective beta-blocking agents on pulse rate of 6 normal subjects following 10 minutes of exercise.[11]

Clearly, the choice of an oculoselective beta blocker addresses concerns that go well beyond achievement of normotension for the typical glaucoma patient in "the age of risk."

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Pseudotumor Cerebri Induced by Danazol

Latif M. Hamed, M.D., Joel S. Glaser, M.D., Norman J. Schatz, M.D., and Thomas H. Perez, M.P.H.

Intracranial hypertension with papilledema occurred in two patients receiving danazol therapy for either cyclic neutropenia or immune hemolytic anemia. Results of clinical, laboratory, and neuroradiologic studies showed no apparent cause for the condition in Case 1 and the papilledema resolved one month after discontinuing danazol. Carotid angiography in Case 2 demonstrated cerebral venous sinus thrombosis; the papilledema showed gradual improvement after cessation of danazol. An additional seven cases of pseudotumor cerebri presumed secondary to danazol therapy have been reported to the Food and Drug Administration. The papilledema resolved in all seven cases soon after discontinuing danazol. A drug-induced complication should be suspected, and alternative therapy sought, in patients who develop intracranial hypertension associated with administration of danazol.

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Orbital Hemorrhage and Eyelid Ecchymosis in Acute Orbital Myositis

David M. Reifler, M.D., Douglas Leder, D.O., and Todd Rexford, B.S.

We examined two patients with acute orbital myositis associated with orbital hemorrhage and eyelid ecchymosis. Both patients were young women (aged 22 and 30 years) who had painful proptosis, diplopia, and computed tomographic evidence of single extraocular muscle involvement with spillover of inflammatory edema into the adjacent orbital fat. Patient 1 showed contralateral preseptal eyelid inflammation and did not suffer an orbital hemorrhage until after an episode of vomiting. In Patient 2, the diagnosis of occult orbital varix was initially considered but an orbital exploration and a biopsy specimen showed no vascular anomaly. Both patients were treated successfully with high-dose systemic corticosteroids. Some cases of idiopathic orbital inflammation may be related to preexisting vascular anomalies or orbital phlebitis.

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Effect of Various Doses of Radiation for Uveal Melanoma on Regression, Visual Acuity, Complications, and Survival

Nadine A. Kindy-Degnan, M.D., Devron H. Char, M.D., Joseph R. Castro, M.D., Stewart Kroll, M.A., Robert D. Stone, M.D., Jeanne M. Quivey, M.D., Theodore L. Phillips, M.D., and Alexander R. Irvine, M.D.

We reviewed 284 choroidal and ciliary body melanomas treated with 50, 60, 70, or 80 gray equivalents (GyE) of helium ion radiation. Multivariate methods of data analysis were used to adjust for differences between dose groups with respect to the characteristics of patients (and their tumors). Radiation dose level did not affect survival, complications, visual outcome, or tumor regression in this model. The minimum radiation dose necessary to achieve tumor control with charged particles may be less than 50 GyE.

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Seven Cases of Trilateral Retinoblastoma

Samuel R. Pesin, M.D., and Jerry A. Shields, M.D.

Of 245 consecutive children with retinoblastoma referred to the Oncology Service at the Wills Eye Hospital between January 1974 and August 1988 and followed up for three months to 15 years, seven (3%) developed midline intracranial malignancies consistent with the diagnosis of trilateral retinoblastoma. Six of the seven had bilateral retinoblastoma, and four had a family history of retinoblastoma. The time of diagnosis of retinoblastoma varied between five months after the intracranial tumor was diagnosed and four years before the intracranial tumor was diagnosed. The midline intracranial malignancies were pineal tumors (five cases), suprasellar neuroblastoma (one case), and a parasellar undifferentiated calcified mass (one case). Despite control of the intraocular tumors, five of the seven children have died of the intracranial tumors.

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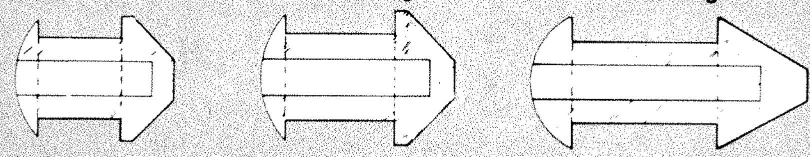

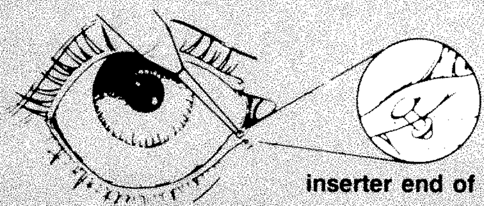

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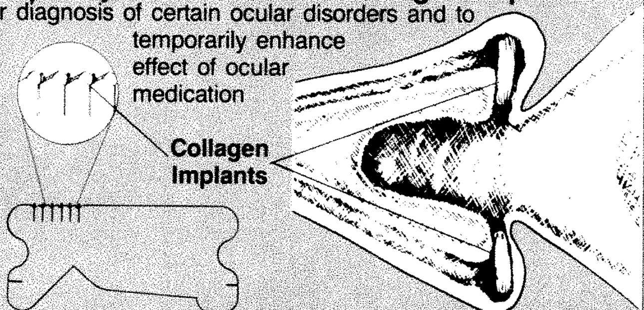

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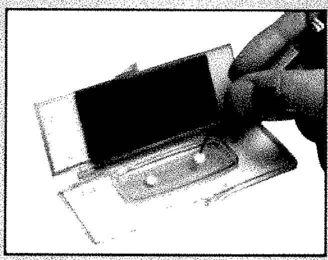

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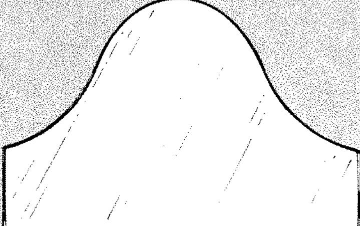

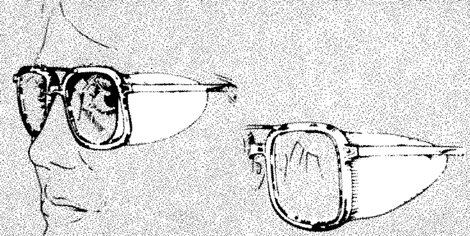

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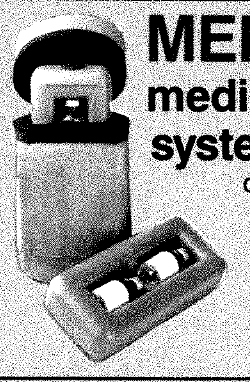

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Immunohistochemical Staining of Sebaceous Cell Carcinoma of the Eyelid

David C. Herman, M.D., Chi-Chao Chan, M.D., George B. Bartley, M.D., Robert B. Nussenblatt, M.D., and Alan G. Palestine, M.D.

We characterized the inflammatory infiltrate of two sebaceous cell carcinomas of the eyelid with immunohistochemical staining to determine the functional class of the mononuclear cells associated with the tumor. The results were compared with the inflammatory infiltrate associated with basal cell carcinomas. The subepithelial spaces and the area immediately surrounding the sebaceous cell neoplasms were free of mononuclear inflammatory cells, in contrast to the basal cell tumors, which had large numbers of subepithelial inflammatory cells and inflammatory cells in intimate contact with the neoplastic cells as previously reported. Inflammatory reaction in the sebaceous cell tumor was limited to a T-cell infiltrate surrounding the vessels adjacent to the tumor. The predominant mononuclear inflammatory cell in both the sebaceous cell and the basal cell carcinomas was the T helper cell. The apparent difference in mononuclear cell infiltrate may be a significant factor in the clinical behavior of the tumors.

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Effect of Intracameral Carbachol on Intraocular Pressure After Cataract Extraction

David K. Linn, M.D., Thom J. Zimmerman, M.D., George F. Nardin, M.D., Rudy Yung, M.D., Susan Berberich, M.D., Harvey DuBiner, M.D., and Meg Fuqua, R.N.

Thirty-two patients were randomly assigned to a treatment or a control group to determine the dose-response and duration of action of intracameral carbachol on immediate postoperative intraocular pressure after extracapsular cataract extraction using a viscoelastic substance. Patients in the treatment group received 0.5, 0.25, or 0.1 ml of 0.01% intracameral carbachol. Patients in the control group received 0.1 or 0.5 ml of balanced salt solution. Intraocular pressures of all patients were measured preoperatively and at three, six, 12, 24, and 48 hours postoperatively. The control group as a whole showed a 9.5-mm Hg intraocular pressure rise at three hours, a 10.0-mm Hg rise at six hours, a 9.0-mm Hg rise at 12 hours, and a 7.2-mm Hg rise at 24 hours postoperatively. The group treated with 0.5 ml of carbachol maintained stable intraocular pressures through the 48-hour measurement period. The groups treated with 0.25 and 0.1 ml of carbachol maintained stable intraocular pressures through 24 hours postoperatively. The differences in intraocular pressure were statistically significant for all treated groups through the 24-hour measurement.

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Pseudoglaucomatous Physiologic Large Cups

Jost B. Jonas, M.D., Frank-Michael Zäch, M.D., Gabriele C. Gusek, M.D., and Gottfried O. H. Naumann, M.D.

Using planimetric analysis of stereoscopic optic disk photographs, we studied 21 optic nerve heads of 11 subjects who shared the common feature of optic cups that were larger than the mean + 2 S.D. within the normal population. A comparison of these findings to those of 571 normal optic disks and 706 optic nerve heads in eyes with chronic primary open-angle glaucoma showed the following morphologic characteristics: (1) abnormally large optic disk area (mean ± S.D., 4.49 ± 0.56 mm^2), (2) large cup/disk ratios with the horizontal ratio (0.78 ± 0.03) significantly ($P < .001$) larger that the vertical (0.71 ± 0.03), (3) increased incidence of cilioretinal arteries, (4) normal neuroretinal rim area (2.06 ± 0.35 mm^2), (5) normal neuroretinal rim configuration, inferiorly (0.43 ± 0.08 mm) broader ($P < .001$, Wilcoxon test) than superiorly (0.33 ± 0.06 mm), smallest ($P < .0001$) temporally (0.20 ± 0.04 mm), (6) normal form of zone alpha (irregular hypopigmentation and hyperpigmentation) of the parapapillary chorioretinal atrophy with its widest extension in the temporal horizontal area, (7) no zone beta (visible large choroidal vessels and sclera), (8) normal caliber of the parapapillary retinal vessels, and (9) normal parapillary retinal nerve fiber layer. These characteristics are helpful in the differentiation of primary and secondary large cups.

© American Journal of Ophthalmology 107:137–144, February, 1989

Large Optic Disks in the Marshallese Population

James M. Maisel, M.D., Caryn S. Pearlstein, M.D., William H. Adams, M.D., and Peter M. Heotis, M.P.S.

On routine examination, asymptomatic patients from the Marshall Islands were noted to have large optic disks associated with high cup/disk ratios and normal intraocular pressure. We retrospectively analyzed color fundus photographs of 54 eyes and 22 eyes of 15 patients had optic disks greater than 2.10 mm, or megalopapilla. Of 36 patients with cup/disk ratios exceeding 0.6, 31 (86%) had visual acuities of better than or equal to 20/30. The optic nerve rim and disk areas varied directly as did disk and cup diameters. Three large disks with an 18-year photographic follow-up showed no change. Optic disk characteristics can vary widely among genetically isolated populations.

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2. On the second day, discontinue the previously used agent and continue with TIMOPTIC in the affected eye(s) b.i.d.

How to transfer from several concomitantly administered antiglaucoma agents to TIMOPTIC:

1. If any agent is an ophthalmic beta-adrenergic blocker, discontinue before starting TIMOPTIC.
2. Continue the other agents being used, but add one drop of 0.25% TIMOPTIC to the affected eye(s) b.i.d.
3. On the following day, discontinue one of the other antiglaucoma agents.
4. The remaining antiglaucoma agents may be decreased or discontinued according to the patient's response to treatment.

If clinical response is not adequate:
Dosage may be increased (from the 0.25% solution) by changing to one drop 0.5% TIMOPTIC twice a day in the affected eye(s). Dosages above one drop of 0.5% TIMOPTIC twice a day generally have not been shown to produce further reduction of IOP. If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to one drop once a day in the affected eye(s).

In patients with a history of severe cardiac disease, signs of cardiac failure should be watched for and pulse rates should be checked.

CONTRAINDICATIONS: TIMOPTIC is contraindicated in patients with bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease (see WARNINGS); sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; hypersensitivity to any component of this product.

WARNINGS: As with other topically applied ophthalmic drugs, this drug may be absorbed systemically.

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and, rarely, death in association with cardiac failure, have been reported following administration of TIMOPTIC (see CONTRAINDICATIONS).

Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, TIMOPTIC should be discontinued.

Obstructive Pulmonary Disease: PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (e.g., CHRONIC BRONCHITIS, EMPHYSEMA) OF MILD OR MODERATE SEVERITY, BRONCHOSPASTIC DISEASE OR HISTORY OF BRONCHOSPASTIC DISEASE (OTHER THAN BRONCHIAL ASTHMA OR HISTORY OF BRONCHIAL ASTHMA, IN WHICH 'TIMOPTIC' IS CONTRAINDICATED, see CONTRAINDICATIONS), SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS, INCLUDING 'TIMOPTIC'. However, if TIMOPTIC is necessary in such patients, then the drug should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery: The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine, or levarterenol.

Diabetes Mellitus: Beta-adrenergic blocking agents should be administered with caution to patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents which might precipitate a thyroid storm.

PRECAUTIONS: *General:* Patients who are receiving a beta-adrenergic blocking agent orally and TIMOPTIC should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

Patients should not receive two topical ophthalmic beta-adrenergic blocking agents concurrently.

Because of potential effects of beta-adrenergic blocking agents relative to blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with TIMOPTIC, alternative therapy should be considered.

Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. TIMOPTIC has little or no effect on the pupil. When TIMOPTIC is used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be used with a miotic not alone.

As with the use of other antiglaucoma drugs, diminished responsiveness to TIMOPTIC (Timolol Mal MSD) after prolonged therapy has been reported in some patients. However, in one long-term study in w 96 patients have been followed for at least three years, no significant difference in mean intraocular pres has been observed after initial stabilization.

Drug Interactions: Although TIMOPTIC used alone has little or no effect on pupil size, mydriasis resu from concomitant therapy with TIMOPTIC and epinephrine has been reported occasionally.

Close observation of the patient is recommended when a beta blocker is administered to patients rece catecholamine-depleting drugs such as reserpine, because of possible additive effects and the producti hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotensio

Caution should be used in the coadministration of beta-adrenergic blocking agents, such as TIMOP and oral or intravenous calcium antagonists, because of possible atrioventricular conduction disturbar left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration sh be avoided.

The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may additive effects in prolonging atrioventricular conduction time.

Animal Studies: No adverse ocular effects were observed in rabbits and dogs administered TIMOPTIC cally in studies lasting one and two years respectively.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year oral study of timolol maleate in there was a statistically significant ($p \leq 0.05$) increase in the incidence of adrenal pheochromocytom male rats administered 300 times the maximum recommended human oral dose* (1 mg/kg/day). Si differences were not observed in rats administered oral doses equivalent to 25 or 100 times the maxi recommended human oral dose. In a lifetime oral study in mice, there were statistically significant (p≤(increases in the incidence of benign and malignant pulmonary tumors and benign uterine polyps in fe mice at 500 mg/kg/day, but not at 5 or 50 mg/kg/day. There was also a significant increase in mam adenocarcinomas at the 500-mg/kg/day dose. This was associated with elevations in serum prolactin w occurred in female mice administered timolol at 500 mg/kg, but not at doses of 5 or 50 mg/kg/da increased incidence of mammary adenocarcinomas in rodents has been associated with administrati several other therapeutic agents which elevate serum prolactin, but no correlation between serum prol levels and mammary tumors has been established in man. Furthermore, in adult human female subjects received oral dosages up to 60 mg timolol maleate, the maximum recommended human oral dosage, were no clinically meaningful changes in serum prolactin.

There was a statistically significant increase ($p \leq 0.05$) in the overall incidence of neoplasms in female at the 500-mg/kg/day dosage level.

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse) in the micronuc test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assa to 100 μg/mL). In Ames tests, the highest concentrations of timolol employed, 5000 or 10,000 μg/p were associated with statistically significant elevations ($p \leq 0.05$) of revertants observed with tester s TA100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester s TA100, no consistent dose response relationship was observed, nor did the ratio of test to control revert reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses 150 times the maximum recommended human oral dose.

Pregnancy: Pregnancy Category C: Teratogenicity studies with timolol in mice and rabbits at doses up t mg/kg/day (50 times the maximum recommended human oral dose) showed no evidence of fetal malfo tions. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effect postnatal development of offspring. Doses of 1000 mg/kg/day (1,000 times the maximum recomme human oral dose) were maternotoxic in mice and resulted in an increased number of fetal resorpti Increased fetal resorptions were also seen in rabbits at doses of 100 times the maximum recomme human oral dose, in this case without apparent maternotoxicity. There are no adequate and well-contr studies in pregnant women. TIMOPTIC should be used during pregnancy only if the potential benefit jus the potential risk to the fetus.

Nursing Mothers: Because of the potential for serious adverse reactions from timolol in nursing infan decision should be made whether to discontinue nursing or to discontinue the drug, taking into accoun importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established by adequate and well-contr studies.

ADVERSE REACTIONS: TIMOPTIC Ophthalmic Solution is usually well tolerated. The following adverse r tions have been reported either in clinical trials of up to three years' duration prior to release in 1978 or s the drug has been marketed.

BODY AS A WHOLE: Headache, asthenia, chest pain. CARDIOVASCULAR: Bradycardia, arrhythmia, hy tension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, palpitat cardiac arrest. DIGESTIVE: Nausea, diarrhea. NERVOUS SYSTEM/PSYCHIATRIC: Dizziness, depress increase in signs and symptoms of myasthenia gravis, paresthesia. SKIN: Hypersensitivity, including l lized and generalized rash, urticaria. RESPIRATORY: Bronchospasm (predominantly in patients with pr isting bronchospastic disease), respiratory failure, dyspnea, nasal congestion. ENDOCRINE: Mas symptoms of hypoglycemia in insulin-dependent diabetics (see WARNINGS). SPECIAL SENSES: Signs symptoms of ocular irritation, including conjunctivitis, blepharitis, keratitis, blepharoptosis, decreased neal sensitivity, visual disturbances, including refractive changes (due to withdrawal of miotic thera some cases), diplopia, ptosis.

Causal Relationship Unknown: The following adverse effects have been reported, and a causal relation to therapy with TIMOPTIC has not been established: *Body as a Whole:* Fatigue; *Cardiovascular:* Hyper sion, pulmonary edema, worsening of angina pectoris; *Digestive:* Dyspepsia, anorexia, dry mouth; *Nerv System/Psychiatric:* Behavioral changes including confusion, hallucinations, anxiety, disorientation, vousness, somnolence, and other psychic disturbances; *Skin:* Alopecia; *Special Senses:* Aphakic cys macular edema; *Urogenital:* Retroperitoneal fibrosis, impotence.

The following additional adverse effects have been reported in clinical experience with oral timolol mal and may be considered potential effects of ophthalmic timolol maleate: *Body as a Whole:* Extremity p decreased exercise tolerance, weight loss; *Cardiovascular:* Edema, worsening of arterial insufficiency. R aud's phenomenon, vasodilatation; *Digestive:* Gastrointestinal pain, hepatomegaly, vomiting; *Hematolo* Nonthrombocytopenic purpura; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Pruritus, skin irritat increased pigmentation, sweating, cold hands and feet; *Musculoskeletal:* Arthralgia, claudication; *Nerv System/Psychiatric:* Vertigo, local weakness, decreased libido, nightmares, insomnia, diminished con tration; *Respiratory:* Rales, cough, bronchial obstruction; *Special Senses:* Tinnitus, dry eyes; *Urogen* Urination difficulties.

Potential Adverse Effects: In addition, a variety of adverse effects have been reported with other b adrenergic blocking agents and may be considered potential effects of ophthalmic timolol maleate: *Diges* Mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* Agranulocytosis, thrombocytopenic purp *Nervous System:* Reversible mental depression progressing to catatonia; an acute reversible syndrome c acterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clou sensorium, and decreased performance on neuropsychometrics; *Allergic:* Erythematous rash, fever c bined with aching and sore throat, laryngospasm with respiratory distress; *Urogenital:* Peyronie's disea

There have been reports of a syndrome comprising psoriasiform skin rash, conjunctivitis sicca, otitis, sclerosing serositis attributed to the beta-adrenergic receptor blocking agent practolol. This syndrome not been reported with timolol maleate.

HOW SUPPLIED: TIMOPTIC Ophthalmic Solution, 0.25% and TIMOPTIC Ophthalmic Solution, 0.5%. E are available in 2.5-mL, 5-mL, 10-mL, and 15-mL plastic OCUMETER® ophthalmic dispensers with a c trolled drop tip. **Also Available:** Preservative-free TIMOPTIC in OCUDOSE® (Dispenser) Sterile Ophthal Unit-Dose Dispenser (see separate Prescribing Information).

Storage: Protect from light. Store at room temperature.

*The maximum recommended single oral dose is 30 mg of timolol. One drop of TIMOPTIC 0.5% cont about 1/150 of this dose, which is about 0.2 mg.

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For more detailed information, consult your MSD Representative and the Prescribing Information.
Merck Sharp & Dohme, Division of Merck & Co., Inc., West Point, PA 19486.

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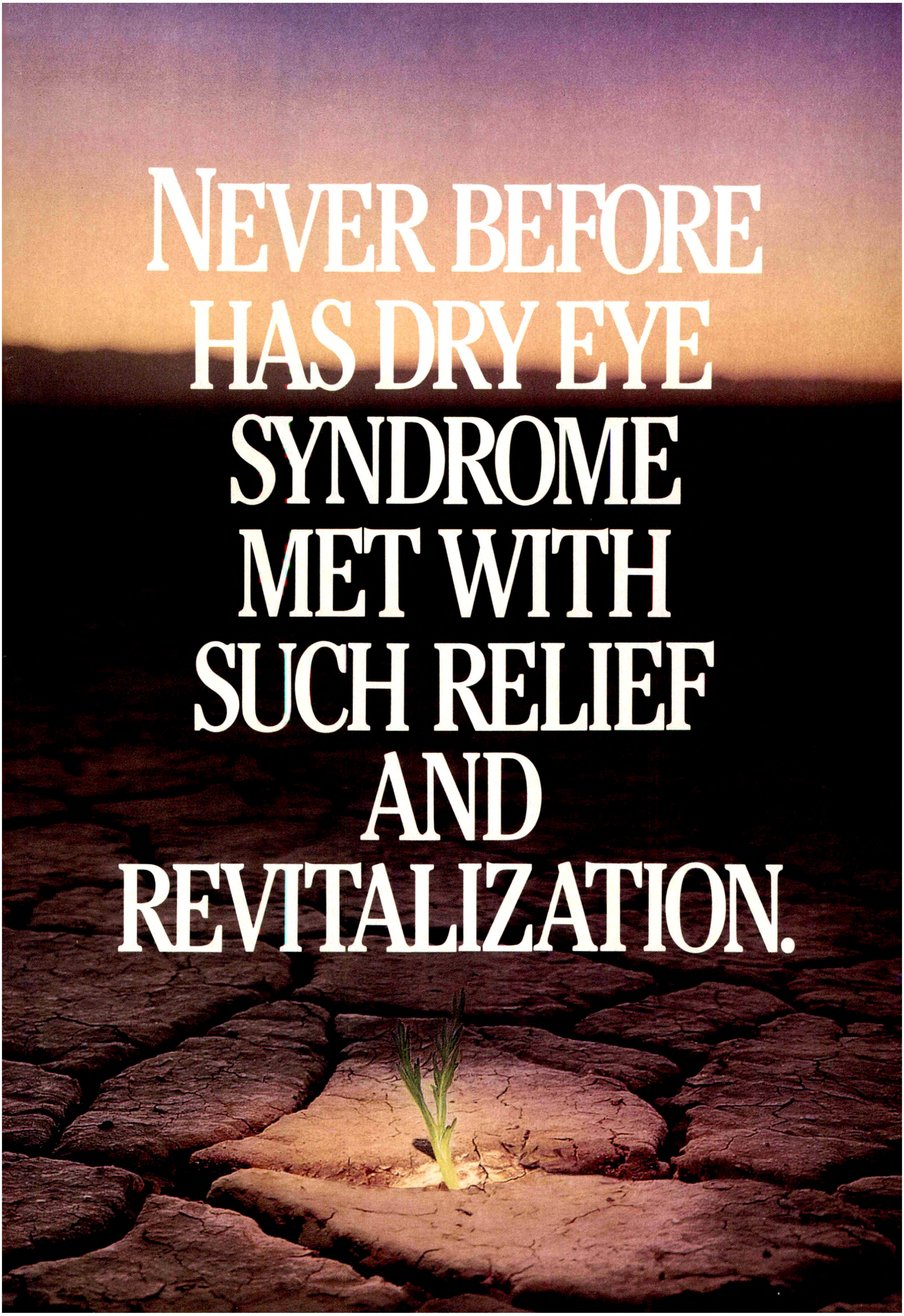
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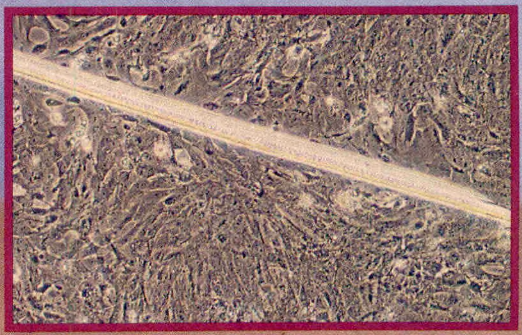

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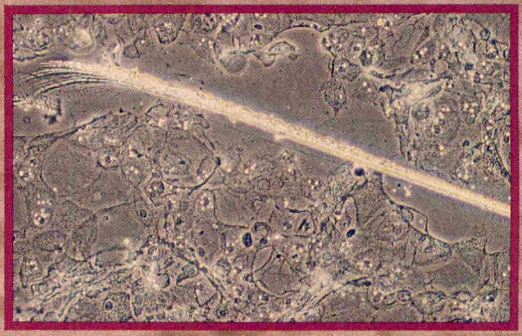
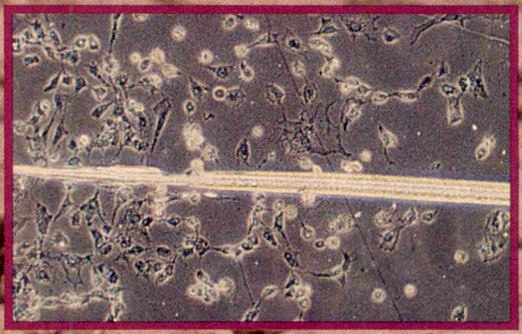
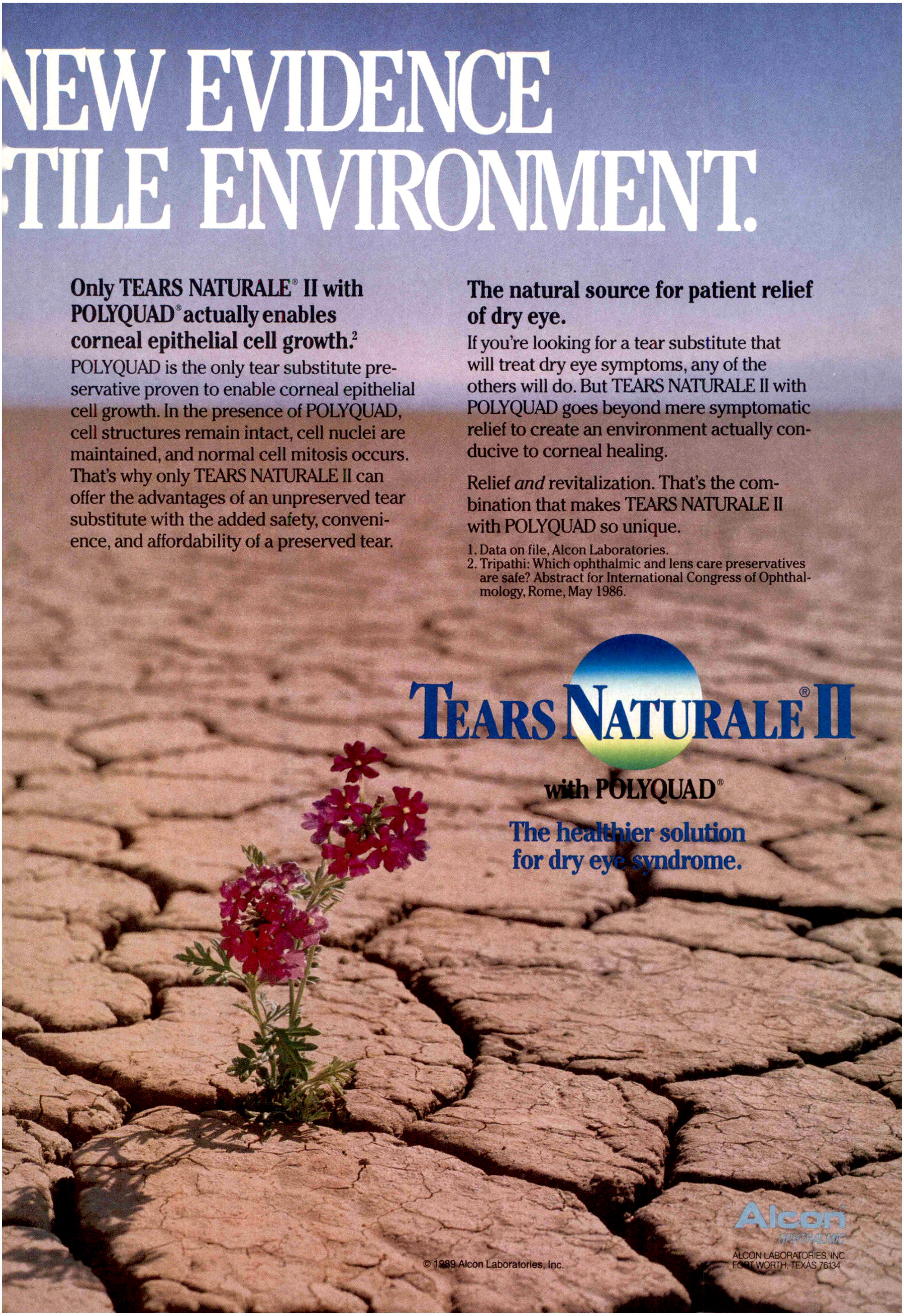


Chlorobutanol 0.5%



Benzalkonium Chloride 0.01%

Phase-contrast microscopy showing primary cultures of human corneal epithelial cells exposed to preservative solutions after 24 hours. Magnified 25X.[1]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The natural source for patient relief of dry eye.
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Relief *and* revitalization. That's the combination that makes TEARS NATURALE II with POLYQUAD so unique.
1. Data on file, Alcon Laboratories.
2. Tripathi: Which ophthalmic and lens care preservatives are safe? Abstract for International Congress of Ophthalmology, Rome, May 1986.
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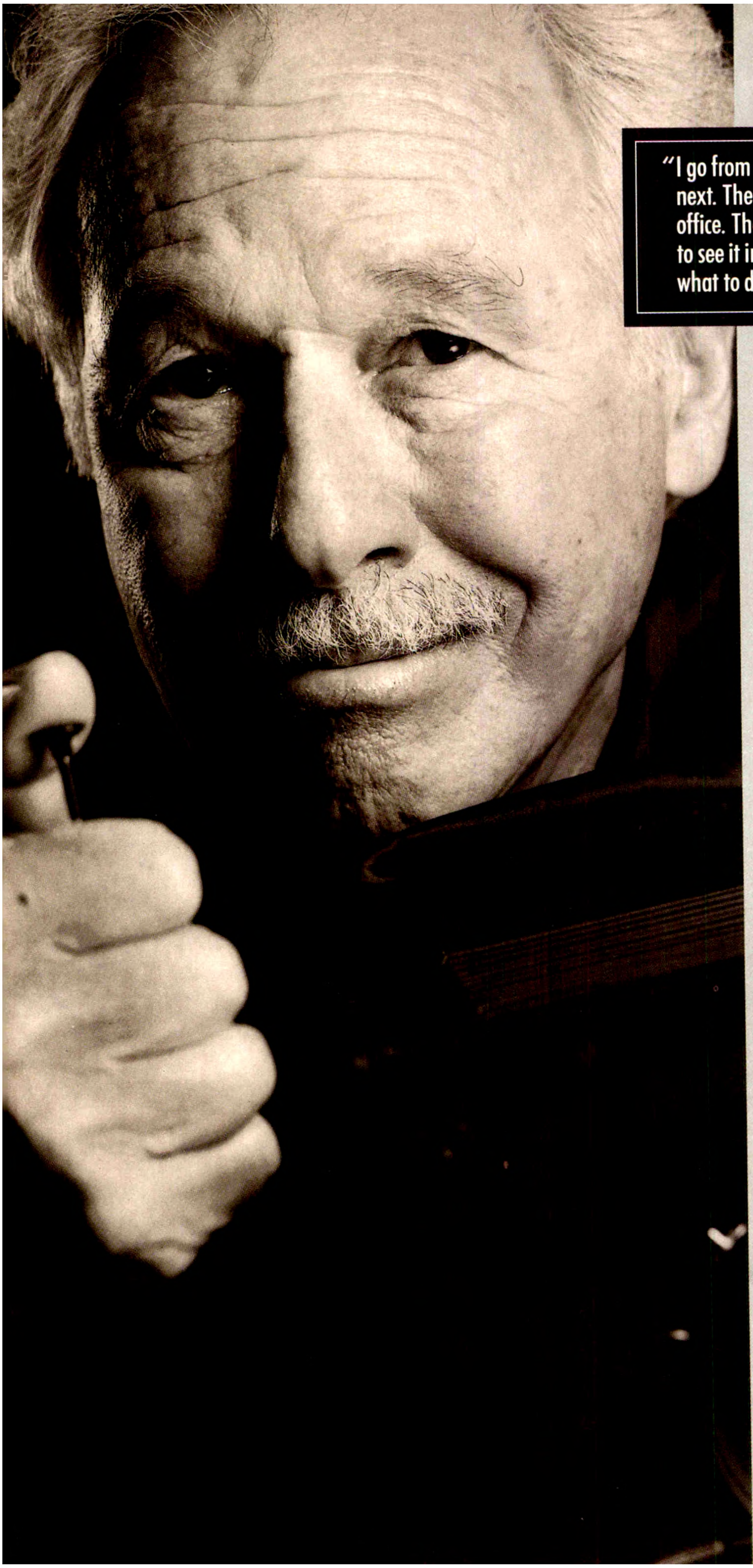

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VOLUME 107 NUMBER 2 FEBRUARY, 1989

Pseudotumor Cerebri Induced by Danazol

Latif M. Hamed, M.D., Joel S. Glaser, M.D., Norman J. Schatz, M.D., and Thomas H. Perez, M.P.H.

Intracranial hypertension with papilledema occurred in two patients receiving danazol therapy for either cyclic neutropenia or immune hemolytic anemia. Results of clinical, laboratory, and neuroradiologic studies showed no apparent cause for the condition in Case 1 and the papilledema resolved one month after discontinuing danazol. Carotid angiography in Case 2 demonstrated cerebral venous sinus thrombosis; the papilledema showed gradual improvement after cessation of danazol. An additional seven cases of pseudotumor cerebri presumed secondary to danazol therapy have been reported to the Food and Drug Administration. The papilledema resolved in all seven cases soon after discontinuing danazol. A drug-induced complication should be suspected, and alternative therapy sought, in patients who develop intracranial hypertension associated with administration of danazol.

DANAZOL is an attenuated androgen derived from ethisterone (17 α-ethinyltestosterone). Although it has been used in the United States for 18 years, the precise mode of action remains unknown. In addition to inhibiting the hypothalamic-pituitary-gonadal axis, it acts by direct enzymatic inhibition of progesterone and androgen binding to cytoplasmic receptors in target tissues. It is metabolized to approximately 60 different products, some of which (for example, ethisterone) may be hormonally active.[1,2]

Danazol is beneficial in the treatment of endometriosis, benign cystic breast disease, hereditary angioedema, precocious puberty, and certain hematologic abnormalities including idiopathic thrombocytopenia purpura and immune hemolytic anemia.[2-4] Side effects of therapy occur in approximately 85% of treated women, and are mostly caused by the anabolic-androgenic properties of the drug. These complications include weight gain (2 to 20 kg), fluid retention, decreased breast size, acne, hirsutism, deepening of the voice, hot flashes, changes in libido, menometrorrhagia, sleep disorders, dizziness, fatigue, tremors, muscle cramps, hepatocellular damage, and headaches.[2,3] In some patients, the headaches may be severe enough to necessitate discontinuation of the drug.[4]

Case Reports

Case 1

A 33-year-old woman was referred for papilledema, headache, and diplopia. At age 16 years, she began to suffer recurrent episodic fever of a few days' duration, associated with profound neutropenia and upper respiratory infections. A bone marrow aspirate obtained during a period of granulocytopenia showed arrest in maturation at the myelocyte stage. A diagnosis of cyclic neutropenia was made. At age 28 years, 200 mg of danazol three times daily provided the patient with hematologic remission. Leukopenia recurred in 1984 when danazol was discontinued, and resolved when it was restarted three months later.

Accepted for publication Oct. 25, 1988.
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The views expressed herein are those of the authors and are not to be construed as official, or as reflecting the views of the Food and Drug Administration.
Reprint requests to Latif M. Hamed, M.D., Bascom Palmer Eye Institute, P.O. Box 016880, Miami, FL 33101.

In October 1987, the patient experienced severe generalized headaches with nausea and vomiting. Horizontal diplopia developed several days later. Bilateral papilledema and a right abducens paresis were noted. Computed tomography of the head showed slit-like ventricles. Results of transfemoral cerebral angiography were normal. A magnetic resonance scan of the head showed partially empty sella. Visual-evoked potentials, brain-stem auditory-evoked potentials, and electroencephalography were normal. A lumbar puncture yielded clear, colorless, acellular cerebrospinal fluid; the protein level was 34 mg/dl and the glucose level was 61 mg/dl. Cerebrospinal fluid cryptococcal polysaccharide antigen and VDRL were negative; there were no malignant tumor cells, fungi, acid-fast bacilli, or microorganisms, and cerebrospinal fluid cultures were negative; myelin basic protein was absent; the opening pressure was not recorded. Serum rheumatoid factor and antinuclear antibodies were negative.

On examination at the Bascom Palmer Eye Institute on Nov. 18, 1987, she weighed 75 kg and her blood pressure was 124/78 mm Hg. The patient was receiving 200 mg of danazol three times daily. Visual acuity was 20/20 at distance and near in each eye. A typical spasm of the near reflex was present. Results of biomicroscopy and tension by applanation tonometry were normal. Tangent screen visual field testing showed moderately enlarged blind spots bilaterally. Ophthalmoscopy showed mild bilateral papilledema (Fig. 1). Standardized A-scan orbital echography showed moderate bilateral enlargement of the optic nerves, measuring 4 mm each (normal mean, 2.8 mm; upper limits of normal, 3.3 mm). There was a positive 30-degree test, indicative of increased subarachnoid fluid in the nerve sheaths associated with papilledema.[5]

Danazol was discontinued and 500 mg of acetazolamide twice a day was begun. One week later, a lumbar puncture showed an opening pressure of 180 mm H_2O. Results of complete cerebrospinal fluid studies were again normal. Acetazolamide therapy was then discontinued. Examination four weeks after discontinuing danazol showed total resolution of the papilledema. On March 10, 1988, spasm of the near reflex was still present, but the papilledema and associated headaches had resolved.

Case 2

A 19-year-old man was referred for headache and transient obscurations of vision. In January 1983, he developed progressive fatigue and jaundice. A diagnosis of warm antibody immune hemolytic anemia (Coombs positive) was made. The patient's condition improved on a regimen of 100 mg of prednisone daily, but attempts to taper the dosage caused recurrence of significant anemia. In December 1983, 200 mg of danazol three times daily was added to the therapeutic regimen, and prednisone dosage was tapered to as low as 5 mg every other day, with maintenance of hematologic remission. In June 1985, a splenectomy was performed after development of persistently increased liver enzyme levels necessitated cessation of danazol. This provided hematologic control without medication until November 1985, when corticosteroids and danazol were reinstated. In December 1986, the patient began to experience frequent generalized headaches, nausea, and transient obscurations of vision.

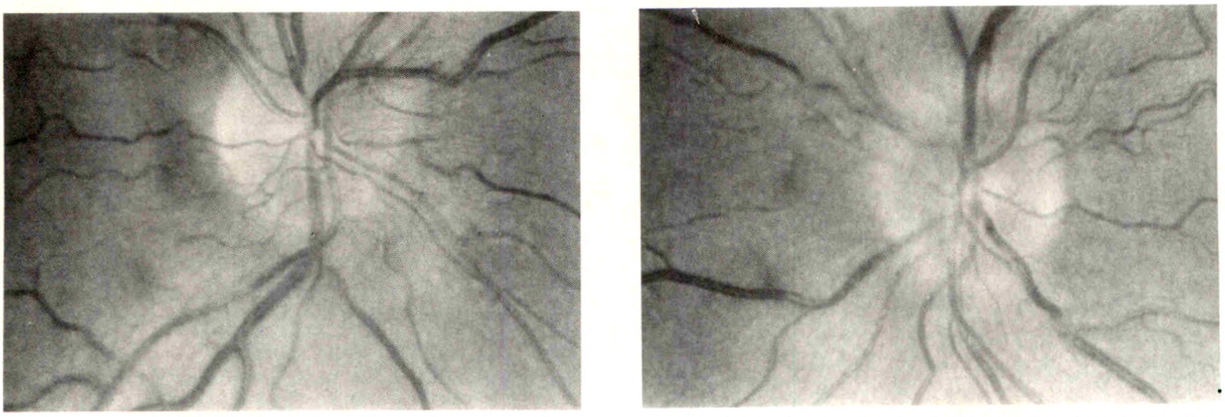

Fig. 1 (Hamed and associates). Patient 1. Left, Right eye; right, left eye. Fundus photographs showing mild bilateral papilledema while the patient was receiving danazol.

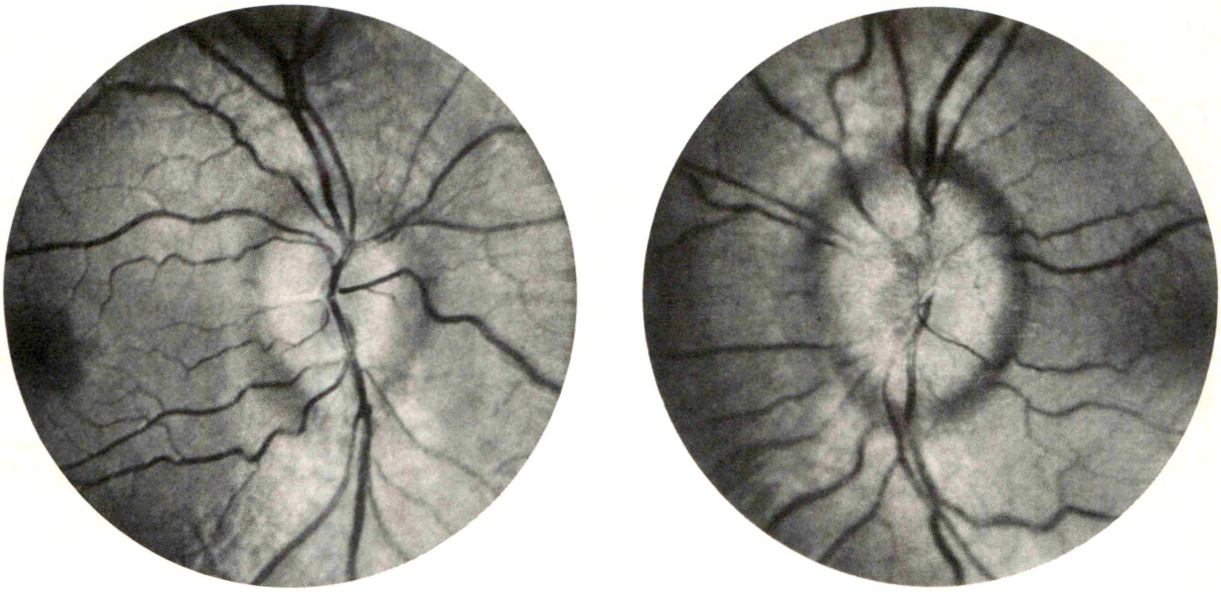

Fig. 2 (Hamed and associates). Patient 2. Left, Right eye; right, left eye. Fundus photographs showing fully developed bilateral papilledema.

He was examined at the Bascom Palmer Eye Institute on May 9, 1987. Blood pressure was 140/80 mm Hg. Daily medications included 10 mg of prednisone and 600 mg of danazol. Visual acuity was 20/20 at distance and near in both eyes. Results of pupillary testing, slit-lamp examination, and tension by applanation tonometry were unremarkable. Goldmann visual fields showed moderately enlarged blind spots bilaterally. There was marked edema of the optic disks bilaterally (Fig. 2). Results of computed tomography of the head were normal. Transfemoral cerebral angiography showed thrombosis of the anterior sagittal sinus, cerebral veins, and straight sinus. The patient declined a lumbar puncture. Acetazolamide, 500 mg, twice daily was added to his regimen. The papilledema remained stable over the next six months.

On Jan. 22, 1988, danazol therapy was stopped. The hematologic status remained in remission during a follow-up period of three months. The papilledema showed gradual improvement over the same period.

Discussion

Pseudotumor cerebri is a syndrome complex characterized by increased intracranial pressure, normal cerebrospinal fluid composition, normal results of neuroradiologic studies, and signs and symptoms strictly referrable to intracranial hypertension. No cause is found in most cases. Some cases, however, are attributed to identifiable conditions including endocrine and metabolic disorders, impairment of cerebral venous outflow (for example, cerebral venous sinus thrombosis), certain systemic illnesses (for example, blood dyscrasias), and exogenously administered agents.[6] The latter is a growing list of drugs that includes corticosteroid therapy or withdrawal,[7-9] nalidixic acid,[10,11] hypervitaminosis or hypovitaminosis A,[12,13] nitrofurantoin,[14] tetracyclines,[15,16] oral contraceptives,[17] psychotherapeutic drugs,[18,19] anti-inflammatory agents,[20,21] and, more recently, the anti-arrhythmic agent amiodarone.[22,23]

Three cases of intracranial hypertension attributed to danazol therapy have recently been reported.[24] Two of the patients received danazol therapy for endometriosis and one for irregular menses and menorrhagia. Papilledema was observed three, six, and eight months after starting danazol treatment. Upon cessation of danazol, one patient showed spontaneous resolution of the papilledema five weeks later and two patients showed full recovery with diuretic therapy. In one patient, headaches and diplopia recurred when danazol was restarted, and resolved upon its cessation.

Seven cases of pseudotumor cerebri associated with danazol therapy have also been reported to the Food and Drug Administration

TABLE

CLINICAL FEATURES OF SEVEN CASES OF PSEUDOTUMOR CEREBRI ASSOCIATED WITH DANAZOL THERAPY REPORTED TO THE FOOD AND DRUG ADMINISTRATION BETWEEN JANUARY 1983 AND APRIL 1988*

PATIENT NO., AGE (YRS), SEX	INDICATION	DURATION† (MOS)	REPORTED DIAGNOSIS	TOTAL DAILY DOSE (MG)	RECOVERY UPON CESSATION
1, 29, F	Endometriosis	0.5	Pseudotumor cerebri	900–1,500	Yes
2, 28, F	Endometriosis	11	Pseudotumor cerebri	400	Yes
3, 58, F	Endometriosis	6	Pseudotumor cerebri	400	Yes
4, 32, F	Endometriosis	6	Papilledema	?	Yes
5, 23, F	Endometriosis	6	Papilledema	400–800	Yes
6, ?, F	Endometriosis	3	Papilledema	800	Yes
7, 32, F	Endometriosis	6	Papilledema	800	Yes

*? indicates data not available.

†Duration reflects the length of drug therapy before onset of reaction.

(Table). Pseudotumor cerebri was the reported diagnosis in three cases and papilledema was the diagnosis in four cases. The papilledema resolved in all seven patients shortly after discontinuing danazol.

Diagnosis of pseudotumor cerebri with certainty requires demonstration of increased intracranial pressure. Although the opening pressure in our first patient was 180 mm H_2O, it was measured one week after starting acetazolamide and discontinuing danazol therapy. The presence of headache, bilateral disk edema, enlarged blind spots, enlarged optic nerves on A-scan echography with a positive 30-degree test (indicative of increased subarachnoid fluid),[5] slit-like ventricles on computed tomography, and a partially empty sella on magnetic resonance imaging constitute strong corroborative evidence that intracranial hypertension was present. Spontaneous resolution of the papilledema shortly after cessation of danazol supports the pathogenetic role of the drug.

Idiopathic intracranial hypertension (pseudotumor cerebri) typically afflicts obese females, often in the third decade of life.[25] Since most patients receiving danazol are women of child-bearing age who are being treated for endometriosis or benign breast disease, the intracranial hypertension in this group of patients may be attributable to the usual idiopathic variety of pseudotumor cerebri rather than a complication of danazol administration. Danazol-induced weight gain and edema may further render such patients similar in body habitus to the prototypical patients afflicted with idiopathic pseudotumor cerebri. Intracranial hypertension caused by danazol may also respond favorably to therapeutic agents beneficial in idiopathic pseudotumor cerebri (for example, carbonic anhydrase inhibitors),[24] thus further confounding the distinction. Moreover, headaches and visual disturbances are cited frequently in patients taking danazol. In some instances these symptoms may be caused by undiagnosed intracranial hypertension. These factors may explain, at least in part, the lack of reports of this side effect.

Decreased cerebrospinal fluid absorption by the arachnoid granulations is currently the most widely accepted pathophysiologic mechanism for pseudotumor cerebri,[26-28] although cerebrospinal fluid hypersecretion[29] or abnormalities of the microvasculature[30] have also been proposed. The mechanism of intracranial hypertension associated with danazol administration is unknown. The heterogeneity of the disorders treated with danazol, and hence the diverse pathogenetic substrates with which the drug may variably interact, suggest that more than one mechanism may be contributory. Cerebral venous thrombosis was present in one of our two patients. Induction of weight gain and fluid retention with danazol therapy may alter cerebrospinal fluid homeostatic mechanisms leading to intracranial hypertension in predisposed individuals. Alternatively, intracranial hypertension may result from a heretofore undefined endocrine effect of danazol or one of its metabolites.

Cerebral venous sinus thrombosis in patients

with immune hemolytic anemia is rare.[31-33] We believe danazol therapy played a role in the occurrence of this complication in Case 2. There have been no previous reports of cerebral venous thrombosis as a complication of danazol, but other androgens have been implicated. Headaches and papilledema have been observed in some patients treated with androstane,[34] testosterone,[35] and oxymetholone,[36] but the mechanism of this complication was not elucidated. In one patient, cerebral venous sinus thrombosis occurred during a hematologic recovery period while receiving 6-mercaptopurine and high doses of adrenocorticosteroids for immune hemolytic anemia.[31] The thrombosis gradually subsided following a reduction in the doses of these drugs. The authors speculated that drug-induced acceleration of hematopoiesis might have resulted in a hypercoagulable state leading to thrombosis. In this regard, danazol has been shown to increase the platelet count, factors VIII and IX, and the kallikrein inhibitor in humans.[37] Of 27 patients with hypoplastic anemia treated with male hormone (fluoxymesterone) or protein-assimilating hormone, three developed superior sagittal sinus thrombosis.[38] After cessation of the hormonal therapy, the condition subsided in all three patients. The authors argued that a thrombogenic action of androgens may be linked to their structural similarity to estrogens and the ability of androgens to function as weak estrogens, the latter having been shown to increase blood coagulability and cause endothelial proliferation and intimal hyperplasia in cranial blood vessels.

Danazol may stimulate circulating immune complex production, complement synthesis, and platelet production, thereby providing additional substrate for thrombosis. Fretwell and Altman[39] described a patient who showed exacerbation of a lupus-like illness while receiving danazol therapy. They speculated that stimulation of complement synthesis by danazol might have provided additional substrate for the immune complex disease. Guillain-Barré syndrome occurred in one patient receiving danazol for hereditary angioedema, and a similar mechanism for this complication was suggested.[40] Steinberg and associates[41] argued that many variables can influence the outcome of sex hormone therapy of autoimmune disease (for example, hormone dosage, age, and genetic background of the recipient), thus making it difficult to predict an outcome in any single patient.

Intracranial hypertension induced by danazol appears to respond favorably to cessation of the drug or diuretic therapy, or both. Given the increasing widespread use of danazol, intracranial hypertension should be noted as an uncommon, but potentially serious, complication.

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Orbital Hemorrhage and Eyelid Ecchymosis in Acute Orbital Myositis

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We examined two patients with acute orbital myositis associated with orbital hemorrhage and eyelid ecchymosis. Both patients were young women (aged 22 and 30 years) who had painful proptosis, diplopia, and computed tomographic evidence of single extraocular muscle involvement with spillover of inflammatory edema into the adjacent orbital fat. Patient 1 showed contralateral preseptal eyelid inflammation and did not suffer an orbital hemorrhage until after an episode of vomiting. In Patient 2, the diagnosis of occult orbital varix was initially considered but an orbital exploration and a biopsy specimen showed no vascular anomaly. Both patients were treated successfully with high-dose systemic corticosteroids. Some cases of idiopathic orbital inflammation may be related to preexisting vascular anomalies or orbital phlebitis.

ORBITAL MYOSITIS is a subtype of the orbital pseudotumor (nonspecific orbital inflammatory) syndrome in which one or more of the extraocular muscles are primarily infiltrated by an inflammatory process.[1,2] Initial features of acute orbital myositis may include pain, diplopia, proptosis, blepharoptosis, conjunctival chemosis, and injection over the involved extraocular muscles. We studied two cases of acute orbital myositis associated with orbital hemorrhage and eyelid ecchymosis.

Accepted for publication Nov. 29, 1988.
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Case Reports

Case 1

A 22-year-old woman was referred for management of "right orbital cellulitis." She had a one-week history of a left upper eyelid "stye," but had developed contralateral painful orbital swelling and diplopia. The patient was afebrile and the white blood cell count was 10,100/mm^3 with a normal differential. The patient was hospitalized and started on intravenous antibiotics. At the time of initial consultation there was 3 mm of proptosis, limited abduction, and chemosis of the right eye, as well as vasocongestion overlying the insertion of the right lateral rectus muscle. On palpation, the edematous left upper eyelid had a firm, rubbery consistency.

A clinical diagnosis of orbital pseudotumor was favored. Computed tomographic scans showed enlargement of the right lateral rectus muscle and an infiltrating mass in the left upper eyelid (Fig. 1). That evening, after a brief episode of emesis, the patient experienced a right orbital hemorrhage with bulbar and upper eyelid involvement (Fig. 2). A regimen of systemic high-dose prednisone was begun, and the pathologic orbital findings resolved as the corticosteroids were tapered and discontinued.

Case 2

A 30-year-old woman developed acute painful left proptosis of 5.5 mm, with lateral displacement of the left eye. The ductions of the left eye were limited and the patient had diplopia in all fields of gaze. Subcutaneous ecchymosis was present in the medial aspect of the left upper eyelid and more superficial, darker ecchymosis was present in the medial left lower eyelid (Fig. 3). The patient was afebrile and the white blood cell count was 12,000/mm^3 with a

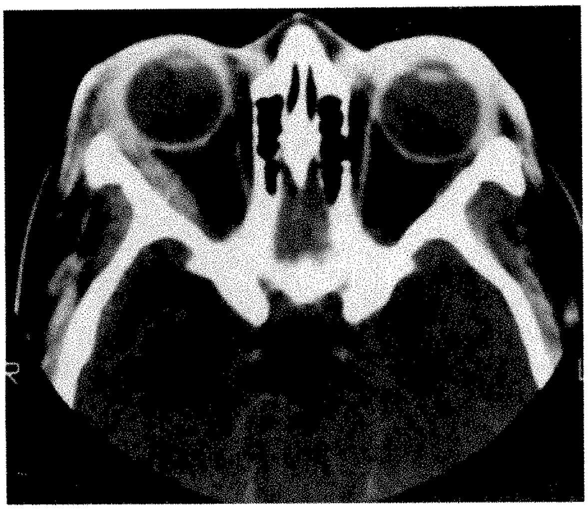

Fig. 1 (Reifler, Leder, and Rexford). Case 1. Computed tomographic scan showing right lateral rectus muscle enlargement and left upper eyelid infiltration.

normal differential. The patient was hospitalized and begun on intravenous ceftriaxone. Computed tomography showed infiltration in the left medial orbit involving the insertion of the medial rectus muscle. A round, radiodense lesion was identified within the area of the inflammation, suggesting possible phlebolith formation (Fig. 4). The patient showed mild progression of the proptosis and a left orbital exploration and biopsy was performed the day after admission. No venous abnormalities or phleboliths were identified at the time of surgery. A biopsy specimen of the orbital fat showed scattered inflammatory cells consistent with orbital pseudotumor. A regimen of oral prednisone was begun, and the inflammation

Fig. 2 (Reifler, Leder, and Rexford). Case 1. Acute orbital myositis with spontaneous right orbital hemorrhage extending anteriorly into the bulbar conjunctiva and right upper eyelid. Left upper eyelid erythema and a subcutaneous mass are also present.

Fig. 3 (Reifler, Leder, and Rexford). Case 2. Acute orbital myositis in a 30-year-old woman with proptosis and ecchymoses of the left lower and upper eyelids.

and proptosis resolved completely without residual motility disturbance. The prednisone was tapered and subsequently discontinued over six weeks.

Discussion

Trauma is the most common cause of orbital hemorrhage and eyelid ecchymosis.[3] Other causes of spontaneous orbital hemorrhage and

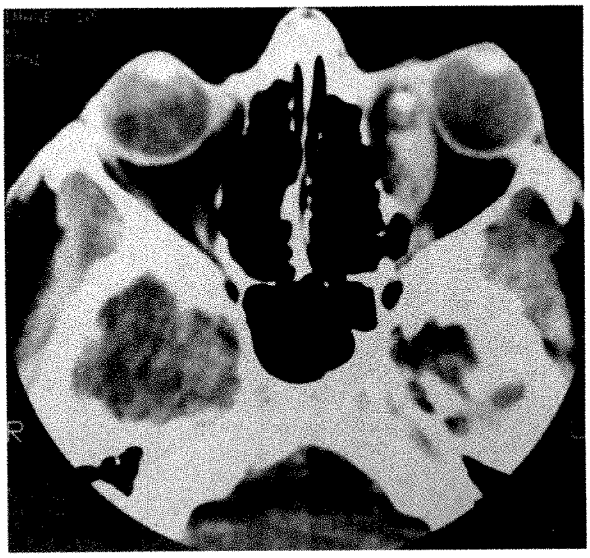

Fig. 4 (Reifler, Leder, and Rexford). Case 2. Computed tomographic scan showing proptosis and spillover of left medial rectus muscle inflammation into the surrounding orbital fat. Focal radiodense area adjacent to infiltrated left medial rectus tendon correlated with pseudoencapsulated orbital hemorrhage found at surgical exploration, but a phlebolith was not found.

eyelid ecchymosis include orbital vascular anomaly, lymphangioma, hypertension, various bleeding disorders, metastatic neuroblastoma, and Valsalva maneuver.[4-6] In both of our cases, acute proptosis preceded the hemorrhage, although emesis also occurred in Case 1.

Eyelid ecchymosis was noted by Krohel and Wright[4] in eight of 17 cases of spontaneous orbital hemorrhage. Eleven of their 17 patients had an underlying vascular malformation. In posterior orbital hemorrhage, eyelid ecchymosis may not appear until the proptosis gradually resolves and blood tracks forward into the anterior orbit.[7] In our patients, eyelid ecchymoses occurred concurrently with proptosis in one case and within 24 hours of documented proptosis in the other case. Perhaps the anterior involvement of the extraocular muscle tendons and the overlying conjunctiva allowed hemorrhage to appear in the eyelids relatively early after the development of acute proptosis.

The cause of orbital hemorrhage in our patients may have been a combination of inflammatory changes in the orbital circulation and mechanical stresses produced by sudden proptosis. Using orbital venography, Kennerdell[8] noted that orbital pseudotumor is occasionally associated with venous abnormalities that are characteristic of inflammation. While orbital vascular anomalies have been demonstrated by orbital venography,[4,7] this technique may fail to demonstrate small or even moderate sized lesions,[8] and its use has been supplanted by computed orbital tomography.

Idiopathic orbital inflammation and orbital vascular anomaly may share certain clinical features including sudden proptosis, edema, and hemorrhage. In some cases, occult orbital vascular anomalies may be associated with phlebitis, resulting in alterations of vascular permeability and secondary edema. In other cases an orbital varix may be readily identified by computed tomography or magnetic resonance imaging. We propose that some cases diagnosed as "idiopathic orbital inflammation" may be related to preexisting vascular anomalies or orbital phlebitis.

Spontaneous orbital hemorrhage may be seen in a variety of primary orbital and systemic diseases. The presence of eyelid ecchymosis may provide evidence for the presence of deeper orbital hemorrhage and aid in the differential diagnosis. We believe that acute orbital myositis should be included in the differential diagnosis of conditions that may be associated with spontaneous orbital hemorrhage and eyelid ecchymosis.

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Effect of Various Doses of Radiation for Uveal Melanoma on Regression, Visual Acuity, Complications, and Survival

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We reviewed 284 choroidal and ciliary body melanomas treated with 50, 60, 70, or 80 gray equivalents (GyE) of helium ion radiation. Multivariate methods of data analysis were used to adjust for differences between dose groups with respect to the characteristics of patients (and their tumors). Radiation dose level did not affect survival, complications, visual outcome, or tumor regression in this model. The minimum radiation dose necessary to achieve tumor control with charged particles may be less than 50 GyE.

IONIZING RADIATION has been used to treat eyes with uveal melanomas since 1929, but the optimum radiation dose remains unknown.[1-6] Stallard[1] pioneered uveal melanoma radiation with ^{60}Co radioactive plaque brachytherapy; however, no dose-response data were generated to establish radiation treatment parameters. Empiric doses of 70 to 140 Gy of ^{60}Co brachytherapy have been delivered to the tumor apex. Most of Stallard's patients received approximately 100 Gy of apical irradiation and this dose has been accepted for conventional radioactive plaque therapy of uveal melanoma.[1] Significant complications associated with uveal melanoma radiation have been reported, including retinal hemorrhages, hard exudates, cotton-wool spots, microaneurysms, optic disk swelling or atrophy, eye wall necrosis, cataract, and neovascular glaucoma.[7-13]

Optimum radiation treatment would encompass a dose level that maximized tumor control and minimized complications. We analyzed retrospectively the effects of 50, 60, 70, or 80 gray equivalents (GyE) of helium ion radiation to determine the relative efficacy and morbidities in patients in each dose group.

Accepted for publication Nov. 8, 1988.

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This study was supported in part by National Institutes of Health grant EYO 7504, American Cancer Society grant PDT-321, unrestricted grants from the Richard and Gail Siegal Foundation, the Beal Foundation, the Northern California Oncology Group, National Institutes of Health grant CA 19138, and Department of Energy contract DE-AC03-76SF00Q98.

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Patients and Methods

All patients were examined in the Ocular Oncology Unit, University of California, San Francisco, and treated between January 1978 and October 1987 at the Lawrence Berkeley Laboratory. Complete follow-up data were available on over 95% of the patients through March 1988.

The diagnosis of uveal melanoma was established on the basis of complete clinical, fluorescein, and ultrasonographic examinations. A metastatic evaluation was performed and included liver function tests, chest roentgenogram, and general physical examinations. Any abnormal findings were subject to further studies.

After informed consent was obtained, patients were treated. The sex and age distributions were comparable in all groups. Between 1978 and 1987, 284 patients were treated with 50, 60, 70, or 80 GyE of helium ion radiation in

five fractions over eight days. Twenty-nine patients received 50 GyE, 61 patients 60 GyE, 122 patients 70 GyE, and 72 patients 80 GyE.

The first 68 patients were treated with 70 GyE. We then studied the next 72 patients at the 80-GyE level of helium ion radiation between 1980 and 1985. Patients were treated with 60 GyE between 1982 and 1986; more recently some tumors over 18 mm in diameter and over 12 mm thick have also been treated at the 60-GyE dose level. Patients with tumors that involved the macula and were not anterior to the equator were treated with 50 GyE since 1983. Fifty-four patients have been treated with 70 GyE since 1985 as part of a randomized prospective study comparing helium ion with ^{125}I plaque irradiation of melanomas less than 15 mm in diameter and less than 10 mm thick.

The entire tumor and a 2-mm surround of presumably normal tissue were included in the treatment field. The details of treatment planning have previously been described.[14]

Patients were examined six to 12 weeks after treatment, then quarterly for one year and semiannually thereafter, unless problems (pain, visual loss, possible tumor growth) occurred. In the interval between our examinations, most patients were followed up by their referring ophthalmologists; any patient with recurrent problems was referred for further evaluation. These examinations included automated and manual visual acuities, automated perimetry, clinical drawings, fluorescein angiography, and ultrasound.

Serious radiation sequelae (radiation retinopathy, radiation optic neuropathy, neovascular glaucoma, cataracts, eye wall necrosis, and loss of eye), minor complications (eyelash loss, keratitis, epiphora), tumor regression rate, visual acuity, and survival rate were analyzed in relation to radiation dose, tumor size, tumor location, and length of follow-up. These tumor characteristics and complications were documented by clinical examination, quantitative echography, and fluorescein angiography. Univariate analyses were initially used; however, the radiation groups were disparate in the tumor thickness, tumor location, and length of follow-up (Table 1). Tumor characteristics were similar in the 60- to 80-GyE treatment groups. Smaller posterior pole tumors were treated with 50 GyE, since initially a high incidence of radiation maculopathy was noted for macular tumors treated at higher dose levels. Treatment groups were analyzed with the Cox multivariate proportional hazards model, when modeling the time until the onset of an untoward event (treatment complication, metastases, or death). Tumor regression rates and changes in visual acuities were analyzed with multiple linear regression, using the covariates discussed and the length of follow-up.

Results

Tumor size was slightly smaller in the 50-GyE treatment group, and most of these tumors involved the fovea (Table 1). Patients in the other treatment groups had tumors of similar size, however, mean length of follow-up was disparate. Seven eyes (2.5%) had small growing tumors, 91 eyes (32.0%) had medium-sized tumors, and 186 eyes (65.5%) had large tumors (Table 2). In 149 eyes (52.5%) the uveal melanomas were located within 3 mm of the optic nerve or fovea. In 164 eyes (57.7%) the anterior edge of the tumor was anterior to the equator.

Tumor regression—Most treated tumors showed tumor shrinkage on the basis of results of clinical, photographic, and ultrasonographic examinations. For purposes of numerical analyses, the initial and most recent echographic and clinical measurements of tumor diameter and thickness were used to calculate percentage of shrinkage. Multiple linear regression was used to model both the amount and percentage of shrinkage. Explanatory variables included in this analysis were clinical tumor diameter, ultrasound tumor height, tumor location, tumor distance from the nerve and the fovea, location of the anterior margin of the tumor, patient age and sex, radiation dose, and length of follow-up. No discernible radiation effect was observed with these multivariate analyses for either the incidence, amount, or rate of regression (Table 3). Initial tumor thickness and length of follow-up were significant independent variables that correlated with both the amount and percentage of shrinkage ($P < .0005$) in all cases. The larger tumors shrank more in absolute and percent terms.

Visual acuity—Multiple linear regression was used to model the change in visual acuity. Similar covariates as listed above were used as explanatory factors. After controlling for the initial visual acuity and the length of follow-up, ultrasound height ($P = .0000$), largest tumor diameter ($P = .003$), location of anterior border ($P = .002$), and distance from fovea ($P = .05$) were independent risk factors for change in

TABLE 1
TUMOR SIZE, LOCATION, AND LENGTH OF FOLLOW-UP

	DOSE OF HELIUM ION RADIATION			
	50 GyE (N = 29)	60 GyE (N = 61)	70 GyE (N = 122)	80 GyE (N = 72)
Largest diameter of tumor (mm)				
Mean	10.1	12.0	12.1	11.7
Range	6.0–18.0	5.0–20.0	5.0–24.0	4.5–20.0
Ultrasound height (mm)				
Mean	5.3	7.2	7.0	6.3
Range	2.5–13.0	3.1–13.8	2.3–14.7	1.3–12.3
Location				
Anterior to equator	8 (27.6%)	35 (57.3%)	73 (59.8%)	48 (66.7%)
≤ 3 mm from nerve	26 (89.7%)	29 (47.5%)	63 (51.6%)	31 (43.1%)
Length of follow-up (mos)				
Mean	26	34	23	48
Range	2–50	2–56	1–99	3–82

visual acuity. The irradiation dose (50 to 80 GyE) was not a significant variable in the visual prognosis (Table 4). The apparent poorer visual results in the 50-GyE group were related to the tumor location in this group; 26 (89.7%) of the tumors were within 3 mm of visually vital structures.

Complications—The Cox multivariate proportional hazards model showed that the risk of developing radiation retinopathy, radiation optic neuropathy, neovascular glaucoma, significant cataracts, and minor complications was not affected by the helium ion radiation dose. The same covariates were used as for evaluating tumor regression. Tumor size (ultrasound height and diameter) and distance from the fovea or optic nerve were consistent correlates of radiation-induced complications ($P < .05$).

Enucleation was performed on 32 (11.2%) patients. In 24 of these patients (75%), the enucleations were performed for a painful blind eye secondary to uncontrollable neovascular glaucoma or sclerokeratitis (Table 5). Eyes with the largest tumors were more likely to undergo enucleation ($P < .03$). Radiation dose did not influence the time to enucleation in the Cox proportional hazards model.

Tumor control—Failure of tumor control manifested either by continued or recurrent growth occurred in 2.5% (seven of 284) cases. Two were medium-sized tumors and five were large tumors (Table 6). As previously described, two cases were considered technical failures and five were radioresistant tumors.[15] These seven patients received 60, 70, or 80 GyE of helium ion radiation. The tumors in two additional eyes, which were initially considered biologic failures, were found to be inapparent diffuse melanomas on histopathologic examination. These were not considered technical treatment failures.

Metastasis—Of 284 patients, 35 had metastases; 27 patients (9.5%) treated with helium ion radiation died of metastatic disease. Mean survival in this group after irradiation was 35.9 months (range, 2.8 to 82.6 months). Tumor thickness and largest tumor diameter were both important variables affecting the survival ($P = .0377$ and $P = .0166$, respectively). Twenty-four of the lethal uveal melanomas (88.9%) were large and 19 (70.3%) extended

TABLE 2
TUMOR SIZE VS RADIATION DOSE

	TUMOR SIZE*			
RADIATION DOSE	SMALL	MEDIUM	LARGE	TOTAL
50 GyE	2	17	10	29
60 GyE	0	17	44	61
70 GyE	3	32	87	122
80 GyE	2	25	45	72
Total	7	91	186	284

*Small, < 3 mm in height and < 10 mm in diameter; medium, 3 to 5 mm in height and 10 to 15 mm in diameter; large, > 5 mm in height or > 15 mm in diameter.

TABLE 3
TUMOR REGRESSION

TYPE OF REGRESSION	DOSE OF HELIUM ION RADIATION 50 GyE (N = 29)	60 GyE (N = 61)	70 GyE (N = 122)	80 GyE (N = 72)
Largest diameter				
No. (%) of tumors showing regression	14 (48.3%)	34 (55.7%)	55 (45.1%)	42 (58.3%)
Onset (mos)				
Mean	7	9	8	9
Range	1–21	1–40	1–83	0.5–47
Ultrasound height				
No. (%) of tumors showing regression	23 (79.3%)	48 (78.8%)	95 (77.9%)	65 (90.3%)
Onset (mos)				
Mean	8	8	6	5
Range	2–24	2–29	1–27	1–24

anterior to the equator (Table 7). Cox multivariate proportion hazards analysis showed that radiation dose did not correlate with time to death from metastatic disease.

Discussion

The optimum radiation dose to achieve tumor control and minimize complications for uveal melanomas is unknown despite over 50 years of use.[1-13] Three factors make a lucid review of the literature on radiation for uveal melanoma difficult. First, the definition of tumor control has been controversial. Secondly, only recently have computer models allowed for accurate ocular isodose calculations, and thirdly, most series have reported a limited radiation dose range. Despite these limitations, determination of an optimum radiation dose for excellent tumor control with decreased morbidity is important both for use of irradiation alone or in conjunction with other treatments.

Historically, many clinicians believed that only complete disappearance of a tumor was

TABLE 4
VISUAL ACUITY

VISUAL ACUITY	DOSE OF HELIUM ION RADIATION* 50 GyE	60 GyE	70 GyE	80 GyE
Initial				
20/15–20/40	8/27	41/61	78/120	46/71
20/50–20/100	6/27	15/61	25/120	19/71
20/200–hand motions	13/27	5/61	16/120	6/71
LP/NLP	0/27	0/61	1/120	0/71
After ≥ 3 years of follow-up				
20/15–20/40	1/10	9/30	7/11	10/35
20/50–20/100	0/10	2/30	1/11	5/35
20/200–hand motions	7/10	13/30	3/11	17/35
LP/NLP	2/10	6/30	0/11	3/35

*Fractions represent number of patients/total number of patients.

TABLE 5
REASON FOR ENUCLEATION

RADIATION DOSE	NO.	%	REASON (NO.)
50 GyE	1	3.5	Vitreous hemorrhage, pain (1)
60 GyE	8	13.1	Neovascular glaucoma (6), keratitis (1), no light perception (1)
70 GyE	13	10.6	Neovascular glaucoma (7), regrowth (4), no light perception (1), vitreous hemorrhage (1)
80 GyE	10	13.9	Neovascular glaucoma (5), keratitis (1), regrowth (2), cataract (1), scleritis (1)

TABLE 6
FAILURE OF TUMOR CONTROL

RADIATION DOSE	NO.	MEAN (RANGE) TIME AFTER THERAPY (MOS)	TUMOR SIZE MEDIUM	TUMOR SIZE LARGE	METASTASES/ DEATH
50 GyE	—	—	—	—	—
60 GyE	—	—	1	—	—
70 GyE	4	26 (14–90)	—	4	2
80 GyE	2	22 (5–39)	1	1	2

synonymous with radiation success. Most ocular oncologists now agree that the goal of ocular radiation is to destroy the reproductive integrity of tumor cells.[4-6] Most radiation damage is manifest when cells enter mitosis. The onset of clinically detectable radiation response is partially dependent on the proliferative rate of tumor cells; faster growing tumors probably shrink more rapidly.[16] Uveal malignant melanomas have a relatively small number of cycling cells as manifested by DNA synthesis phase analysis, using bromodeoxyuridine studies.[17] Stallard[1] believed that results of evaluation four to six months after irradiation were usually an accurate means to predict the success or failure of the treatment. We now realize that tumor regression is often delayed for many months, and that tumor size also has a marked effect on the degree of shrinkage. After either proton or helium ion radiation the mean latency of detectable tumor shrinkage is 12 months; all recurrences after charged-particle irradiation have been noted in less than 36 months after treatment. Irradiated small uveal melanomas will often regress to a flat chorioretinal scar; however, the efficiency of intraocular tumor debris removal is limited, and larger tumors only partially regress. The earliest sign of successful irradiation is usually the loss of subretinal fluid, followed by a decrease in tumor thickness and a dark gray appearance of the melanoma remnant. Overall, most irradiated melanomas have approximately 40% shrinkage in thickness five years after irradiation.[5,6,18]

We have studied nongrowing or regressed irradiated large melanomas either at autopsy or after enucleation because of complications resulting from radiation. Most tumors had substantial bulk but did not have mitotic figures or evidence of cycling cells based on 5-bromo-2'-deoxyuridine studies.[17,19-21] These data help to substantiate the concept that the goal of radiation for uveal melanomas is to destroy their reproductive integrity, even though irradiated tumor cells may appear structurally viable.

The advent of computer programs for radiation dosimetry has revolutionized treatment planning for uveal melanoma therapy. Many of the early studies were reported before the use of such programs and the accuracy of their dose calculations is questionable. There has also been a trend to treat much larger tumors than previously. Most of Stallard's uveal melanomas were small- to medium-sized, and over 85% (63 of 72) had partial tumor regression using 70 to 140 Gy at the tumor apex.[1] In our series over 65% of uveal melanomas were large and after treatment with 50 to 80 GyE of helium ions, over 97% had good tumor control. Similar results have been noted with other radiation modalities. Shields and coworkers[6] reported the results of the first 100 uveal melanomas irradiated with an average of 80 Gy to the tumor apex with ^{60}Co brachytherapy. Tumor control was achieved in 96% of cases and, unlike earlier brachytherapy reports, only seven melanomas were small. Gragoudas and

TABLE 7
METASTATIC DEATH

RADIATION DOSE	NO.	%	MEAN (RANGE) TIME AFTER THERAPY (MOS)	TUMOR SIZE MEDIUM	TUMOR SIZE LARGE	LOCATION* ANTERIOR	LOCATION* POSTERIOR
50 GyE	1	3.5	37	1	—	—	1
60 GyE	3	4.9	32 (23–42)	—	3	2	1
70 GyE	7	5.7	36 (14–67)	2	5	5	2
80 GyE	16	22.2	39 (3–59)	—	16	12	4
Total	27	9.5	36 (3–67)	3	24	19	8

*Anterior, anterior to equator; posterior, posterior to equator.

coworkers[18] irradiated 128 melanomas (94% were medium- or large-sized tumors) with 70 GyE of proton radiation and all tumors showed some regression. Total regression occurred in 12% of their cases.

In this study with multivariate analysis, lower radiation doses (50 GyE) did not affect tumor control, complication rates, or survival. None of 29 eyes treated at a 50-GyE radiation dose had evidence of continued tumor growth. The mean follow-up period in this group of patients was 26 months, and it is highly doubtful that any of these treated patients will show recurrence or tumor reactivation with further follow-up. The rationale for using higher radiation doses is uncertain. While a few studies have been performed at substantially higher radiation doses, only anecdotal reports exist at lower treatment levels.[22,23] The minimum radiation dose necessary to achieve tumor sterility is unknown. Our helium ion data showed over 97% tumor control at doses as low as 50 GyE. Sealy and associates[23] reported two cases of tumor regression after 36 and 38 Gy of ^{125}I brachytherapy to the tumor apex; the length of follow-up was 42 and eight months, respectively. We have managed one melanoma with documented growth after it was treated erroneously elsewhere as a choroidal metastasis with 27 Gy of photon radiation.

Lower radiation doses using either charged-particle or brachytherapy approaches may decrease the incidence of radiation-induced vasculopathy. A number of centers have begun studies combining hyperthermia with radiation to achieve tumor control with fewer ocular complications than occur with radiation alone.[24,25] To accomplish this goal, four conditions must be met. One, there should be an additive or synergistic effect of radiation and hyperthermia; some human and animal data support this concept.[26] Two, a much lower dose of radiation in combination with hyperthermia must be sufficient to produce tumor control, so that radiation complications can be reduced. Our study suggests that significantly lower radiation dosages than have been tried should be used if this goal can be achieved. Three, the effect of the combined treatments on tumor tissue must be greater than the damage produced in normal tissue (thermal enhancement ratio); data supporting this concept are not conclusive.[26] Finally, the hypothesis that lower doses of radiation may result in a lower incidence of ocular morbidity must be correct. It is conceivable that the radiation dose may not be a major factor in all of the ocular morbidity observed after treatment. Untreated uveal melanomas can be associated with neovascular glaucoma, retinal neovascularization, inflammation, and cystoid macular edema.[27] In both the proton and helium ion studies we have observed significant visual loss due to factors that occur outside of the radiation field.[28] For example, thick equatorial tumors can be associated with an exudative maculopathy that appears to correlate with tumor size and is not associated with radiation to the fovea. This type of data would be consistent with an alternative hypothesis that intrinsic tumor factors, both during growth and regression, can produce ocular morbidity. If this latter hypothesis is responsible for a significant portion of the posttreatment visual loss, then strategies such as combination hyperthermia and lower-dose radiation would not be effective.

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OPHTHALMIC MINIATURE

Munch was inspired to paint this picture *(Melancholy [Laura] 1899)* after seeing his sister again who had suffered from severe depression since her childhood; several sketches show her empty look with widely opened eyes, cut off from the world, lost in herself. Munch's convalesence in a sanitorium also played a role in the creation of this painting. There Munch noted: "When the winter sun which lay low on the horizon shone through the window—the room was ablaze with red and yellow—The yellow wooden walls turned into fire and the brown ceiling became blood—The light and the colors penetrated my soul and my body, in which my sick blood flowed. Melancholy . . . I ran out to escape the eerie creature."

Uwe M. Schneede, *Edvard Munch. The Early Masterpieces*
Munich, Schirmer/Mosel, 1988

Seven Cases of Trilateral Retinoblastoma

Samuel R. Pesin, M.D., and Jerry A. Shields, M.D.

Of 245 consecutive children with retinoblastoma referred to the Oncology Service at the Wills Eye Hospital between January 1974 and August 1988 and followed up for three months to 15 years, seven (3%) developed midline intracranial malignancies consistent with the diagnosis of trilateral retinoblastoma. Six of the seven had bilateral retinoblastoma, and four had a family history of retinoblastoma. The time of diagnosis of retinoblastoma varied between five months after the intracranial tumor was diagnosed and four years before the intracranial tumor was diagnosed. The midline intracranial malignancies were pineal tumors (five cases), suprasellar neuroblastoma (one case), and a parasellar undifferentiated calcified mass (one case). Despite control of the intraocular tumors, five of the seven children have died of the intracranial tumors.

THE ASSOCIATION of a midline intracranial neoplasm with retinoblastoma has become well known over the past decade. This association has been termed "trilateral retinoblastoma,"[1,2] since this condition occurs most often in patients with bilateral retinoblastoma. The retinoblastoma gene is believed to confer an increased susceptibility to developing these intracranial tumors,[1,2] which most often are undifferentiated neuroblastic pineal tumors and suprasellar or parasellar neuroblastomas.[1,2]

In our search of the literature, we found fewer than 40 reported cases of midline intracranial neoplasms associated with retinoblastoma, most of which are in the form of case reports.[2-10] The early series by Bader and associates[1] detailed experience with their own cases as well as those of other investigators. The most recent report by Kingston, Plowman, and Hungerford[11] reviewed all patients within two institutions to determine who developed trilateral retinoblastomas. A review of reported cases from various institutions has been recently compiled by Zimmerman.[12] Of 245 patients referred to our institution for primary treatment of retinoblastoma between January 1984 and August 1988, seven developed a midline intracranial neoplasm. Two of these patients (Patients 1 and 2) have been previously described.[4]

Case Reports

Case 1

At 6 weeks of age, this girl was found to have bilateral retinoblastomas. Her father had bilateral sporadic retinoblastomas. Each eye of the child received external beam radiation, xenon photocoagulation, and cryotherapy. At 8 months of age, a cobalt 60 plaque was applied to the right eye to treat residual tumor. At 32 months of age, she was found to have a right mandibular metastasis from her retinoblastoma, which was treated with radiotherapy and chemotherapy with cyclophosphamide and vincristine. No other metastases were found, and the retinoblastomas in both eyes showed excellent regression. At 34 months of age, she was found to have a midline intracranial tumor, histologically confirmed as an undifferentiated tumor of the pineal gland (pinealoblastoma). Despite aggressive chemotherapy and craniotomy with excision, she died 22 months later of widespread dissemination of the pineal tumor in the central nervous system.

Case 2

This girl with no family history of retinoblastoma had poor visual fixation at 5 months of age. Computed tomography disclosed a suprasellar mass; the biopsy specimen showed a

Accepted for publication Nov. 11, 1988.

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neuroblastoma. Indirect ophthalmoscopy at that time disclosed a normal fundus in both eyes. The brain tumor was treated with cranial radiotherapy and intrathecal chemotherapy. On follow-up ophthalmoscopy five months later, bilateral retinoblastomas were diagnosed, with three tumors in the right eye and two tumors in the left, all of which were less than 3.0 mm in diameter and 0.5 mm thick. These were controlled with external beam radiotherapy (4,000 cGy in each eye). Despite the aggressive treatment of her neuroblastoma, she died at 15 months of age from continued proliferation of the intracranial tumor.

Case 3

This girl was examined at 1 week of age because her father and sibling had bilateral retinoblastomas. At that time, her right eye was found to contain a small retinoblastoma, which was less than 3.0 mm in diameter and 1.5 mm thick. Seven weeks later, two small retinoblastomas were found in her left eye, both measuring less than 1 mm in diameter and 0.25 mm in thickness. Each eye received 4,000 cGy of external beam radiation. At 5 months of age, she was found to have almost complete regression in the right eye and no evidence of tumors in the left eye. She did well until 36 months of age, when she complained of headaches. On ocular examination, she had bilateral papilledema but no change in her regressed retinoblastomas. Computed tomography showed hydrocephalus with a pineal mass. After diagnostic craniotomy, the pineal neoplasm was unsuccessfully treated with chemotherapy and radiotherapy, and she died at 43 months of age.

Case 4

This boy with no family history of retinoblastoma was found to have unilateral retinoblastoma in the right eye at 1½ months of age, with a single tumor 8 mm in diameter and 5 mm in thickness located temporal to the macula. He was treated with an iridium 192 plaque and did well initially. Eleven months later, the retinoblastoma had enlarged, and he received a cobalt 60 plaque. Each plaque delivered 4,000 cGy to the tumor apex. Follow-up computed tomography at age 13 months disclosed a pineal tumor, and the patient died of pineal malignancy at 23 months of age despite control of the intraocular tumor. At age 10 months, his identical twin brother without retinoblastoma had an enlarged head from hydrocephalus, and a pineal neoplasm was diagnosed. He died at 17 months of age as a result of this tumor.

Case 5

This boy had a father and paternal grandmother whose eyes were enucleated because of retinoblastoma. At age 6 months, his right eye was enucleated because of four large tumors (the largest measuring 18 mm in diameter and 12 mm in thickness). No optic nerve invasion or extraocular extension were found on histologic study of this eye. Four months later, his left eye was found to contain a tiny retinoblastoma (1 mm in diameter and 0.25 mm thick), for which he received cryotherapy with an excellent response. At 11 months of age, computed tomography was performed to evaluate increasing somnolence. The scan disclosed a pineal tumor. The patient died at 31 months of age after unsuccessful radiation therapy and chemotherapy for his midline intracranial neoplasm.

Case 6

At 5½ months of age, this girl was found to have bilateral familial retinoblastoma, with three tumors in the right eye (the largest being 10 mm in diameter and 5 mm thick) and one tiny tumor in the left eye (2 mm in diameter and 0.5 mm thick). The girl's mother had undergone bilateral enucleation as an infant for retinoblastomas. Follow-up computed tomography of the child disclosed a large, calcified parasellar soft tissue mass, with third ventricle and cavernous sinus extension but no pineal involvement. She has received cryotherapy to the left eye and external beam radiation to the right eye, with an excellent response. She has undergone excision of the parasellar mass via craniotomy, and histologic studies showed an undifferentiated, markedly calcific tumor. As of November 1988, she is alive at 12 months of age and undergoing radiotherapy and chemotherapy for the brain tumor.

Case 7

At 6 months of age this girl with no family history of retinoblastoma was found to have bilateral retinoblastomas. Her left eye was enucleated because of a large retinoblastoma originating from the posterior pole and comprising over half the vitreous cavity. There was prelaminar optic nerve involvement without tumor invasion into the choroid or posterior to

the lamina cribrosa. Her right eye which contained six tumors received 4,600 cGy of external beam radiation, with a good response. However, one month later, intravitreal extension was noted over two of the tumors, and she received iodine 125 plaque therapy delivering 4,000 cGy to the central axis of the globe. An excellent regression pattern was noted two months later, and the tumors have thereafter remained inactive. At 24 months of age, she developed ataxia and lethargy. Computed tomography disclosed a pineal tumor and hydrocephalus, for which she has undergone a shunting procedure. As of November 1988, she is still alive one month after diagnosis of the intracranial tumor.

Results

Of the seven children, five developed pineal tumors and two developed parasellar tumors (Table). Three of the patients who developed pineal tumors were girls, and both patients who developed parasellar tumors were girls. The age at diagnosis of retinoblastoma varied from 2 weeks to 10 months (average, 4.3 months). Four of the seven children had family histories of retinoblastoma. Six patients had bilateral and one had unilateral retinoblastomas. However, the one patient with unilateral retinoblastoma most certainly represented a germinal mutation, since his twin brother had a pineal tumor without retinoblastoma.[12]

Before diagnosis of the intracranial malignancies, three patients (Patients 1, 3, and 7) received external beam radiotherapy for the retinoblastomas (Table). Three patients (Patients 1, 4, and 7) had received radioactive plaque brachytherapy. Three patients (Patients 2, 5, and 6) had received no radiotherapy. One patient (Patient 2) had developed the intracranial tumor five months before the diagnosis of retinoblastoma, whereas in another patient (Patient 6) the intracranial tumor and retinoblastoma were diagnosed simultaneously.

The time of diagnosis of retinoblastoma varied between five months after and 32 months before the diagnosis of intracranial tumor (mean, 14 months after diagnosis of retinoblastoma). Five of the seven patients have died of their intracranial malignancies. Of these, the time between diagnosis of the original retinoblastoma and death from their second tumor ranged from five to 54 months. The time between diagnosis of the second tumor and death ranged from seven to 22 months. Two patients (Patients 6 and 7) are still alive at 12 and 24 months of age, respectively. However, their prognoses are considered guarded.

Discussion

One of the most recently observed manifestations of the genetic abnormality associated with bilateral retinoblastoma is the occurrence of an undifferentiated midline intracranial neuroblastoma in the pineal, suprasellar, or parasellar regions.[1,3,4,11,12] The designation of trilateral retinoblastoma has been coined for this association.[1,2] However, much less commonly, patients with unilateral retinoblastomas have been reported to develop midline intracranial neoplasms.[1,6,10,12] Furthermore, such an intracranial tumor has also occurred in a family member of a patient with retinoblastoma.[11] These two aforementioned instances have been considered formes frustes of trilateral retinoblastoma.[12]

It is well established that when midline intracranial neoplasms occur in patients with retinoblastoma, they do so overwhelmingly in children with bilateral or the genetic form of retinoblastoma.[11,12] In our series, six of seven patients with midline intracranial tumors had bilateral retinoblastoma. We are aware of seven other cases of midline intracranial tumors associated with a unilateral retinoblastoma.[1,3,6,10-12] Four of these seven were pineal tumors, and the others were suprasellar or parasellar tumors. Six of the seven patients had a family history of retinoblastoma. The one patient with unilateral retinoblastoma with no family history of retinoblastoma developed a parasellar tumor.[6] Our patient (Case 4) with unilateral retinoblastoma and pineal tumor most certainly represented a germinal mutation, since his twin brother developed a pineal tumor.

There has been one previously reported occurrence of a midline intracranial neoplasm in an otherwise unaffected family member of a patient with retinoblastoma. Kingston, Plowman, and Hungerford[11] described a 5-month-old girl with a suprasellar tumor; seven years earlier bilateral retinoblastoma and a suprasellar tumor were diagnosed in her sister. In our series, unilateral sporadic retinoblastoma was diagnosed in a 6-week-old infant (Patient 4).

TABLE
PATIENTS WITH RETINOBLASTOMA AND MIDLINE INTRACRANIAL NEOPLASMS

PATIENT NO.	SEX	AGE AT DIAGNOSIS OF RETINOBLASTOMA AND INITIAL TREATMENT (MOS)	RETINOBLASTOMA LATERALITY	FAMILY HISTORY	MIDLINE TUMOR LOCATION	RETINOBLASTOMA TREATMENT BEFORE DIAGNOSIS OF INTRACRANIAL TUMOR
1	F	1.5	Bilateral	Yes	Pineal	External beam radiation, xenon photocoagulation, and cryotherapy in both eyes; ^{60}Co plaque in right eye
2	F	10.0	Bilateral	No	Suprasellar	None
3	F	0.25	Bilateral	Yes	Pineal	External beam radiation in both eyes
4	M	1.5	Unilateral	No	Pineal	^{192}Ir plaque and ^{60}Co plaque in right eye
5	M	6.0	Bilateral	Yes	Pineal	Right eye enucleated; cryotherapy in left eye
6	F	5.5	Bilateral	Yes	Parasellar	None
7	F	6.0	Bilateral	No	Pineal	Left eye enucleated; external beam radiation and ^{125}I plaque in right eye

*Second tumor identified five months before diagnosis of retinoblastoma.

His identical twin brother, who had normal results on ocular examination, developed a pineal neoplasm at 10 months of age. Three months later, the twin with retinoblastoma was also found to have a pineal tumor. The findings in these cases also resemble those described by Zimmerman[13] and François and colleagues[14] in patients with osteosarcomas, the most common second nonocular primary tumor in retinoblastoma survivors. For example, an osteosarcoma of the femur developed in a patient free of retinoblastoma, but whose sibling had a retinoblastoma transmitted as an autosomal dominant trait.[14]

Zimmerman,[12] in reviewing the literature on midline intracranial neoplasms in patients with retinoblastoma, found that in 27 of 37 patients (73%), the intracranial neoplasm was a pineal tumor; in the remaining ten patients it was a parasellar or suprasellar tumor. Similarly, in our series, five of seven intracranial neoplasms were located in the pineal gland. In comparing the gender of the 37 patients with pineal or parasellar tumors, Zimmerman[12] found that 14 of the 27 patients (51%) with pineal tumors were male and six of the ten patients with parasellar tumors were male. In our study, two of the five patients with a pineal tumor were male.

Zimmerman[12] also compared the age at diagnosis in patients with pineal tumors to that in patients with suprasellar or parasellar tumors. The mean age at diagnosis of pineal tumors in patients with retinoblastoma was 44 months, with diagnosis of the retinoblastomas at a mean age of 7 months. The mean age at diagnosis of parasellar and suprasellar tumors in patients with retinoblastoma was 9 months, with diagnosis of the retinoblastomas at a mean age of 8 months. Of the patients in our series who developed pineal neoplasms, these tumors were identified at a mean age of 23.7 months; the retinoblastomas were identified at a mean age of 3 months. Of the two patients who developed a parasellar or suprasellar tumor, one tumor was found five months before diag-

TABLE *(Continued)*

TIME BETWEEN DIAGNOSIS OF RETINOBLASTOMA AND DIAGNOSIS OF INTRACRANIAL TUMOR (MOS)	TIME BETWEEN DIAGNOSIS OF RETINOBLASTOMA AND DEATH FROM INTRACRANIAL TUMOR (MOS)
32	54
−5*	5
36	43
12	22
5	25
Simultaneous	>7
18	>19

nosis of the retinoblastoma at 10 months of age, and the other was found at the same time as the retinoblastoma at 5½ months of age. Thus, our data are consistent with earlier reports, in that there appears to be a difference in time of diagnosis between the midline intracranial tumors of pineal origin and those of parasellar or suprasellar origin.

Pineal neoplasms, although rare, have been suggested to be the most frequent cause of death during the first decade of life in patients with bilateral retinoblastoma.[11] In the series by Bader and colleagues,[1] most patients treated for pineal tumors died within 15 months after diagnosis. Kingston, Plowman, and Hungerford[11] reported a median survival time of only eight months after diagnosis of the midline intracranial tumor. In our series, the five patients who died of their midline intracranial tumor did so an average of 13 months after diagnosis of that tumor.

Our data suggest that radiation treatment of the retinoblastoma probably does not predispose to the development of midline intracranial neoplasms. Three of the seven patients had no previous radiation therapy, three had local radioactive plaque therapy, and three had external beam radiotherapy. Furthermore, radiation is not known to cause pineal tumors and the parasellar or pineal location of the midline intracranial neoplasm is considered well outside the radiation field.[1] Also, as in our study, this tumor has occurred in patients with retinoblastoma whose family members have developed midline intracranial neoplasms and no retinoblastomas.[11]

There are several arguments against pineal and parasellar tumors being metastatic retinoblastomas. There are no direct vascular or neuronal channels between the retina and the pineal gland.[1] As in Patient 3, these intracranial neoplasms have also been found in patients with tiny, noninvasive retinoblastomas that almost never metastasize.[1,5,11,12] These tumors exhibit striking differentiation, quite uncharacteristic of metastases.[1,5,11,12] When retinoblastomas metastasize, they characteristically produce multiple lesions[5,12]; the pineal gland has not been proven to be a metastatic site of retinoblastoma.[1] Unilateral retinoblastomas occur almost twice as often as bilateral ones, yet most pineal or parasellar tumors are associated with bilateral retinoblastomas.[5,12] Lastly, in all reports of parasellar tumors, this lesion was found before or simultaneous with the retinoblastoma in very young children.[1,5,12]

Many cases of trilateral retinoblastoma were probably not recognized in the past because the midline neuroblastic tumor was interpreted as an intracranial metastasis of retinoblastoma. This seems understandable, since these midline tumors present only a few months to years after diagnosis of retinoblastoma and have a histologic resemblance to retinoblastoma. It is thus not surprising that midline intracranial neoplasms have not been reported in association with retinoblastoma until as recently as 11 years ago. As previously suggested,[1] perhaps a retrospective evaluation of autopsy specimens available from assumed cases of metastatic retinoblastoma might disclose these previously undetected midline intracranial neoplasms.

Midline intracranial neoplasms may also be diagnosed more frequently today because of more advanced diagnostic capabilities, such as computed tomography and magnetic resonance imaging, along with increased awareness of the existence of such tumors in patients with hereditary retinoblastoma. Our Patient 6

exemplifies this latter point whereby once her bilateral retinoblastomas were clinically discovered, a routine brain scan looking specifically for a midline intracranial neoplasm disclosed one.

In light of the deadly nature of the midline intracranial neoplasms associated with retinoblastomas, it is obvious that the most successful treatment would depend on early detection. Thus, as part of the initial investigation of familial or bilateral retinoblastoma, we recommend routine computed tomography or magnetic resonance imaging, or both, with special attention to the pineal gland, suprasellar region, and ventricles. Such a recommendation has also been made by Zimmerman.[12] Furthermore, these patients should routinely be examined for any neurologic signs or symptoms consistent with increased intracranial pressure, including headaches, lethargy, or papilledema. Any such finding should merit immediate repeat brain imaging. It is hoped that earlier recognition and treatment of the intracranial neoplasms in these children will improve the prognosis.

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OPHTHALMIC MINIATURE

Thou who didst come to bring
On thy redeeming wing
  Healing and sight,
Health to the sick in mind,
Sight to the inly blind,
O now, to all mankind,
  Let there be light!

The Hymnal of the Protestant Episcopal Church in The United States of America

Immunohistochemical Staining of Sebaceous Cell Carcinoma of the Eyelid

David C. Herman, M.D., Chi-Chao Chan, M.D., George B. Bartley, M.D., Robert B. Nussenblatt, M.D., and Alan G. Palestine, M.D.

We characterized the inflammatory infiltrate of two sebaceous cell carcinomas of the eyelid with immunohistochemical staining to determine the functional class of the mononuclear cells associated with the tumor. The results were compared with the inflammatory infiltrate associated with basal cell carcinomas. The subepithelial spaces and the area immediately surrounding the sebaceous cell neoplasms were free of mononuclear inflammatory cells, in contrast to the basal cell tumors, which had large numbers of subepithelial inflammatory cells and inflammatory cells in intimate contact with the neoplastic cells as previously reported. Inflammatory reaction in the sebaceous cell tumor was limited to a T-cell infiltrate surrounding the vessels adjacent to the tumor. The predominant mononuclear inflammatory cell in both the sebaceous cell and the basal cell carcinomas was the T helper cell. The apparent difference in mononuclear cell infiltrate may be a significant factor in the clinical behavior of the tumors.

SEBACEOUS CELL CARCINOMA is a rare, malignant tumor that may occur in the ocular adnexa. This neoplasm accounts for 4.7% of all malignant tumors of the eyelids[1] and is characterized by variable clinical appearance, a propensity to recur, and the ability to metastasize and cause death.[1-5] In contrast, basal cell carcinoma, the most common malignant tumor originating on the eyelids, rarely metastasizes.

Attempts have been made to correlate the inflammatory infiltrate surrounding the tumor with prognosis since early in this century.[6-8] The evidence from these studies is often contradictory and, in general, unconvincing.[9] Interpretation of these reports is difficult because the investigators were unable to determine the functional class of the mononuclear cells described. Recent developments in functional typing of inflammatory cells may allow correlation of mononuclear infiltrate with clinical prognosis. To investigate whether differing immune responses may contribute to tumor activity, we used immunohistochemical staining to describe the cellular infiltrate of sebaceous cell carcinomas and basal cell carcinomas originating on the eyelid.

Case Reports

Case 1

A 54-year-old man with metastatic adenocarcinoma of the colon was referred to the National Eye Institute for treatment of a recurrent "chalazion." A chalazion had been removed from the same site approximately one year earlier at another institution.

A firm mass, measuring 3 × 5 × 1.5 mm, with a contiguous symblepharon was present in the lateral right lower eyelid. The periauricular and submandibular nodes were not palpable. The lesion was excised with full-thickness wedge resection of the lateral half of the lower eyelid, and reconstruction was accomplished by primary closure. Light microscopy disclosed a large mass composed primarily of large, oil red O-positive cells with occasional mitotic figures, findings consistent with sebaceous cell carcinoma. No evidence of recurrence was noted at the most recent examination four months postoperatively.

Accepted for publication Nov. 2, 1988.
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Case 2

A 56-year-old woman was seen in January 1984 by her primary ophthalmologist for an enlarging mass near the right caruncle. An excisional biopsy was performed, and the lesion was determined histologically to be a sebaceous cell carcinoma with microscopically tumor-free margins. Periodic follow-up examinations disclosed no evidence of recurrence until January 1987, when a small nodule appeared on the right medial canthus. The mass slowly enlarged during the ensuing six months, and the patient was referred to the Mayo Clinic.

A fleshy, vascular, raised, smooth lesion measuring 6 × 4 mm was present on the nasal right lower eyelid margin, between the lacrimal punctum and the previously excised caruncle. The clinically apparent lesion was excised, and detailed map biopsy specimens were taken from the conjunctiva.[10] Frozen-section analysis confirmed the diagnosis of recurrent sebaceous cell carcinoma. In addition to the eyelid and conjunctival biopsy specimens, several specimens from the anterior orbit were positive for tumor. Computed tomography confirmed invasion of the tumor into the right anterior medial orbit without extension into the ethmoid sinus. A systemic evaluation was negative for metastasis. After validation of the frozen-section interpretation with permanent sections, the right orbit was exenterated and was allowed to heal spontaneously by granulation. No postoperative complications or evidence of tumor recurrence or metastasis was noted during the 15-month follow-up period.

Case 3

A 73-year-old man was examined at the Mayo Clinic for a 10-mm lesion with the classic features of nodular basal cell carcinoma in the left medial canthus. The mass was excised, and frozen histologic sections confirmed the diagnosis of basal cell carcinoma. Tumor-free margins were obtained, and a free skin graft was applied to cover the defect. No evidence of recurrence was noted 18 months after resection.

Material and Methods

After excision, each specimen was snap frozen and embedded in OCT compound. Frozen serial sections, 4 μm thick, were prepared. Immunoperoxidase (avidin-biotin-peroxidase complex) techniques were used.[11] The primary antibodies were monoclonal antibodies prepared against human pan T lymphocytes (Leu-4), T helper/inducer cells (Leu-3a), T helper/inducer cells with inducer function (Leu-8), T suppressor/cytotoxic cells (Leu-2a), T suppressor/cytotoxic cells with suppressive function (Leu-15), B lymphocytes (Leu-14), natural killer cells (Leu-7), macrophages (Leu-M5), anti-HLA-DR (OKIa and HLA-DR), anti-HLA-DQ and monocytes (Leu-10), and Langerhans' cells (OKT6). The presence of Il-2 receptors on lymphocytes (an indicator of T-cell activation) was evaluated using anti-Tac antibody, an antibody specific for the Il-2 receptor. Mouse ascitic fluid containing 1 to 2 μg/ml of protein served as a control. The secondary antibody was biotin-conjugated horse anti-mouse IgG. Avidin-biotin-peroxidase complex solution was then applied; the substrate was diaminobenzide-Ni-H_2O_2. The remaining portions of each tissue specimen underwent routine histopathologic analysis.

The immunohistochemically stained sections were observed in ten separate microscopic fields (magnification, ×40). Cells were considered positive if they showed a dense, dark black-blue peripheral ring of stain on their cellular membrane. After the positive cells stained by each primary antibody were counted, the percentages and ratios expressing the various inflammatory cellular types and subtypes were calculated and recorded.

Results

Cases 1 and 2

Well-demarcated nests of neoplastic cells typical for sebaceous cell carcinoma were apparent in the routine stains in each case. There was nucleus-cytoplasm disproportion, with occasional mitotic figures and faint blue staining of the cytoplasm with hematoxylin and eosin. Staining with oil red O was positive for each of the tumors, and no evidence of epithelial pagetoid changes was apparent. No signs of inflammatory cell invasion into the tumor were seen in either case, although a dermal vasculitis was simulated by a marked number of inflammatory cells surrounding the blood vessels away from the tumor. Few inflammatory cells were noted in the subepithelial spaces surrounding the tumors (Figs. 1 and 2).

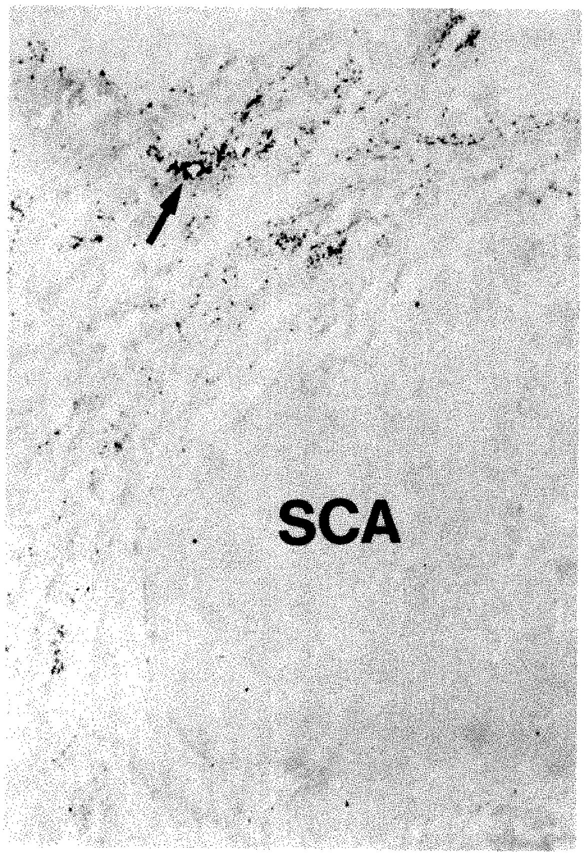

Fig. 1 (Herman and associates). Case 1. Sebaceous cell carcinoma. Large space between tumor (SCA) and mononuclear infiltrate. Note Leu-4+ cells (arrow) surrounding vessel adjacent to tumor (immunoperoxidase Leu-4, ×50).

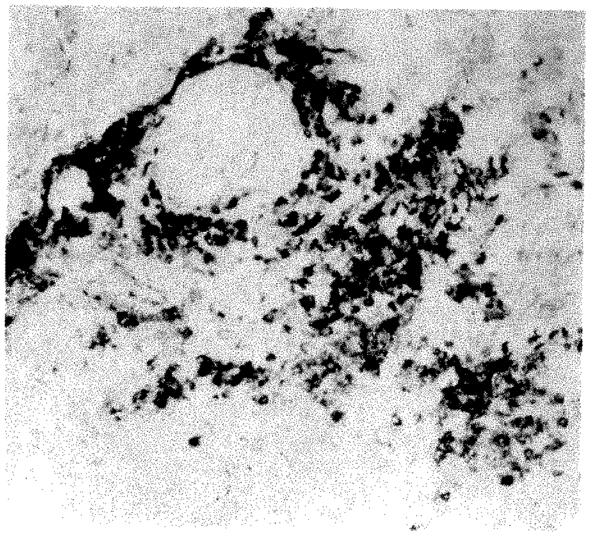

Fig. 2 (Herman and associates). Case 1. Sebaceous cell carcinoma. Most inflammatory cells surrounding the vessels stain positive for T-cell marker (immunoperoxidase Leu-4, ×250).

Immunohistochemical studies disclosed that most of the inflammatory cells around the blood vessels were T lymphocytes (Leu-4+). No T lymphocytes were seen in the tumor itself or in the cords of tissue between the nests of malignant cells. In Case 1, 90% to 95% of the T lymphocytes were T helper cells without inducer function (Leu-3a+ and Leu-8−). The remainder of the lymphocytes were suppressor/cytotoxic cells with suppressive function (Leu-2a+ and Leu-15+). In Case 2, the ratio of T helper to T suppressor cells was 1:1. In both cases, 40% to 50% of the lymphocytic infiltrate was positive for Il-2 receptor (anti-Tac+), an indication of activated T cells.

There were a few natural killer cells around blood vessels, and an occasional natural killer cell was seen in the tissue surrounding the tumor nests; however, no such cells were identified in the tumor itself. Similarly, there were few macrophages (Leu-M5+) within and around the tumor, but a moderate number were present around the blood vessels in the vicinity of the tumor. Occasional B cells (Leu-14+) were identified around the vessels, but none were found in the tumor itself. The inflammatory cells around the tumor and the adjacent vessels were markedly HLA-DR- (anti-HLA-DR+) and HLA-DQ- (Leu-10+) positive, as was the endothelium of the blood vessels. There was no evidence of HLA-DR or HLA-DQ expression within the tumor substance itself in either case. Staining with OKT6 disclosed few Langerhans' cells in the tissue surrounding the tumors.

Case 3

Hematoxylin and eosin stains of the tissue showed the classic pattern of basal cell carcinoma with palisading basophilic cells in the dermis. In contrast to the sebaceous cell carcinomas, many inflammatory cells surrounded the tumor, some intimately associated with the tumor cells. Large numbers of inflammatory cells were present in the subepithelial areas surrounding the tumor. Few inflammatory cells were found within the tumor itself. In a few areas of necrotic tumor, inflammatory cells were more prevalent. Collections of inflammatory cells around the vessels were not evident.

Immunohistochemical staining showed T lymphocytes (Leu-4+) to be the predominant

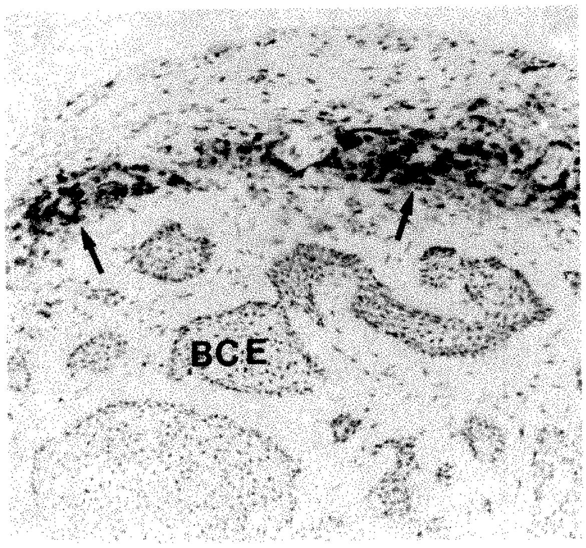

Fig. 3 (Herman and associates). Case 3. Basal cell carcinoma. Mononuclear infiltrate (arrows) located adjacent to tumor (BCE) (immunoperoxidase Leu-4, ×150).

inflammatory cell in the area of the tumor. There were large numbers of T lymphocytes surrounding the tumor and below the normal epithelium in the areas around the tumor (Fig. 3). There were a few T cells within the tumor substance. Of the lymphocytes in the areas around the tumor, 85% to 90% were helper cells (Leu-3a+), and 5% to 10% of the cells in this area were suppressor/cytotoxic cells (Leu-2a+). Suppressor/cytotoxic cells with suppressive function (Leu-15+) were also found around the tumor, and a small number of these cells were located within the tumor substance itself. Seventy to eighty percent of the T cells were positive for Il-2 receptor (Tac+), a higher ratio of activated cells than found in the sebaceous cell carcinoma group. No natural killer cells were found in areas of viable tumor cells. Occasional macrophages (Leu-M5+) were found near the nests of neoplastic cells. B cells were not found in any of the areas around or within the tumor. Cells around the nest of neoplastic cells and the dermis itself were strongly HLA-DR positive. The normal epithelium was also HLA-DR positive. Greater than normal numbers of Langerhans' cells were found in the dermis above and surrounding the tumor by staining with OKT6. A small number of these cells were also found within the nests of tumor cells.

Within necrotic areas of the tumor, the distribution of types of inflammatory cells differed, with T cells primarily of the suppressor/cytotoxic type (70% suppressor/cytotoxic cells and 30% helper cells). The predominant cell type found in the necrotic tumor was the macrophage.

Discussion

Immunohistochemical analysis demonstrated a readily apparent difference in the distribution of inflammatory infiltrate between sebaceous cell carcinoma, a rare, aggressive tumor with metastatic potential, and basal cell carcinoma, a neoplasm that often behaves relatively benignly. The nests of neoplastic basal cells were surrounded by inflammatory cells, predominantly T cells. The immunohistochemical findings were consistent with the results of similar reports that included 86 basal cell carcinomas; therefore, additional basal cell carcinomas were not studied.[12-14] The sebaceous cell tumors showed minimal inflammatory reaction around or inside the nests of neoplastic cells themselves, although many inflammatory cells were identified around the blood vessels in the area of the tumor. The predominant cell type was also the T cell.

In situ immunity in tumors is suggested by the finding that cellular elements constitute the immune response. However, the nature of their function has yet to be elucidated. In some tumor models the presence of an active immune response is clearly associated with tumor rejection, yet in other examples there seems to be no effect on the neoplasm. There is evidence to suggest that some types of immune response to tumor actually may promote neoplastic proliferation.[15]

Host immune response to tumor depends on both the antigenicity of the tumor and the ability of the host to mount the proper immune response.[16] The antigenicity of a tumor is difficult to evaluate, particularly in humans. Studies performed in animals, however, have shown that tumors induced chemically or with ultraviolet light are more immunogenic than tumors that occur spontaneously.[17-20] Support for the antigenicity of skin carcinomas in humans is provided by the observation that sunlight-associated tumors are among the least aggressive neoplasms. Metastasis of nonmelanoma skin tumors is rare and generally occurs late in their clinical evolution.[19] An ina-

bility to mount an adequate immune response may contribute to the increase in otherwise rare neoplastic diseases found in patients who are immunosuppressed[21-24] and those with the acquired immunodeficiency syndrome.[25,26] Restoration of immune competence has been shown to cause regression of tumor in some of these patients.[21,22] Chronic inflammatory cells also may be found in areas subjected to repeated trauma, such as rubbing by the patient or surgical manipulation of the lesion. However, differences in distribution and population of inflammatory cells associated with neoplasms are more likely the result of characteristics of the tumor rather than external physical factors.

Several investigators have found a high incidence of visceral tumors in patients with benign sebaceous cell tumors of the eyelid.[4,27] However, no clinically evident defects in immune function have been reported in these patients. One of our patients (Case 1) had an associated visceral neoplasm, but it is impossible to determine any relationship between the two tumors.

The effect on tumor behavior of the presence or absence of certain functional subtypes of inflammatory cells in tumor infiltrates is unknown. Recently, Claudatus and colleagues[14] compared the inflammatory infiltrates of 22 basal cell carcinomas with those of 30 squamous cell carcinomas. The basal cell and early squamous cell carcinomas showed a predominance of helper cells (T4+) over suppressor cells (T8+), with few natural killer cells (Leu-7+) and no granulocytes. Advanced or metastatic squamous cell carcinomas showed a predominance of suppressor cells (T8+), with many natural killer cells and granulocytes.[14] These data imply that suppressor and natural killer cells may be associated with more aggressive tumors. It is not known whether the presence of these cells increases the proliferative ability of the tumors or is simply a secondary response to aggressive neoplastic behavior. The recurrent sebaceous cell carcinoma in Patient 2 is noteworthy because many more suppressor/cytotoxic cells with suppressive function (Leu-2a+) and natural killer cells were present than in the primary sebaceous cell carcinoma in Patient 1.

The role of immune surveillance in the control of basal cell carcinoma has been inferred indirectly from several different studies. The in vitro cell cycle time of basal cell carcinoma is 217 hours, which would result in a doubling time of only nine days.[28] The in vivo doubling time, however, is measured in months or years, which suggests that factors that inhibit the proliferation of neoplastic cells may be important. Markers of T-cell activation in the infiltrate of T cells associated with basal cell carcinomas were found in our study and others, a finding that implies a role for active cellular immune mechanisms in determining the clinical behavior of the tumor.[12] Basal cell carcinoma, a tumor that is commonly thought to be induced or promoted by exposure to ultraviolet light, possibly is more immunogenic, a trait resulting in a greater number of inflammatory cells surrounding the lesion, than a tumor that occurs spontaneously, such as sebaceous cell carcinoma. In this study, the cellular response differed markedly between the sebaceous cell and basal cell neoplasms, and it may play a role in the clinical behavior of the tumors. It is impossible to state, however, that the apparent difference in immune response is the sole factor responsible for the difference in clinical activity of these two neoplasms.

We hope that this preliminary report will stimulate others to use immunohistochemical methods to study the immune mechanisms associated with rare ophthalmic tumors such as sebaceous cell carcinoma. This technique may be useful for determining factors affecting prognosis and treatment.

ACKNOWLEDGMENT

Ming Ni, M.D., provided assistance with monoclonal staining.

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Effect of Intracameral Carbachol on Intraocular Pressure After Cataract Extraction

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Thirty-two patients were randomly assigned to a treatment or a control group to determine the dose-response and duration of action of intracameral carbachol on immediate postoperative intraocular pressure after extracapsular cataract extraction using a viscoelastic substance. Patients in the treatment group received 0.5, 0.25, or 0.1 ml of 0.01% intracameral carbachol. Patients in the control group received 0.1 or 0.5 ml of balanced salt solution. Intraocular pressures of all patients were measured preoperatively and at three, six, 12, 24, and 48 hours postoperatively. The control group as a whole showed a 9.5-mm Hg intraocular pressure rise at three hours, a 10.0-mm Hg rise at six hours, a 9.0-mm Hg rise at 12 hours, and a 7.2-mm Hg rise at 24 hours postoperatively. The group treated with 0.5 ml of carbachol maintained stable intraocular pressures through the 48-hour measurement period. The groups treated with 0.25 and 0.1 ml of carbachol maintained stable intraocular pressures through 24 hours postoperatively. The differences in intraocular pressure were statistically significant for all treated groups through the 24-hour measurement.

THE EXISTENCE of a considerable rise in intraocular pressure during the early postoperative period after cataract extraction is well established. Hollands, Drance, and Schulzer[1] have recently demonstrated a significant hypotensive effect using acetylcholine during extracapsular cataract surgery. They reported postoperative pressure reductions of approximately 10 mm Hg at three hours and 7 mm Hg at six hours. However, the use of intracameral acetylcholine did not result in statistically significant reductions in intraocular pressure measured at nine and 24 hours postoperatively. In a second study, the same authors found that 0.01% intracameral carbachol in 0.4-ml total volume was highly efficacious in reducing mean intraocular pressures for a full 24 hours postoperatively.[2]

We undertook this study to determine the smallest amount of intracameral carbachol required to prevent postoperative intraocular pressure increases. Our study differed from the two studies by Hollands, Drance, and Schulzer[1,2] in that we used a viscoelastic substance (Healon) intraoperatively as needed.

Material and Methods

There were 32 patients in this study. All patients were men admitted to the Veterans Administration Medical Center for extracapsular cataract extraction and Sinsky-style posterior chamber intraocular lens implantation. Patients with normal preoperative intraocular pressures (less than 22 mm Hg in both eyes) with no clinical evidence of glaucoma were selected. Patients with significant peripheral retinal degeneration or advanced diabetic retinopathy in either eye were excluded. Patients were randomly assigned to two groups. Group 1 consisted of 17 patients who were assigned to either a control group receiving 0.5 ml of balanced salt solution or a treatment group receiving 0.5 or 0.25 ml of 0.01% carbachol intracamerally. Group 2 consisted of 15 patients who were randomly assigned to receive either 0.1 ml of balanced salt solution or 0.1 ml of carbachol intracamerally. All operations in Group 1 were performed by one of us (R.Y.), and all operations in Group 2 were performed by another of us (S.B.). The same preoperative, operative, and postoperative procedures were used throughout the study. Routine patient sedation with methohexital in conjunction with a retrobulbar block was used preoperatively. The ret-

Accepted for publication Nov. 9, 1988.

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robulbar block was given in the standard fashion using 2% lidocaine with epinephrine and 0.75% bupivacaine in a 50/50 mixture with 100 units of hyaluronidase. Preoperative pupil dilation was accomplished using 2% phenylephrine and 1% tropicamide, one drop every five minutes times three. Constant pressure was applied with a Honan balloon at 30 mm Hg for 30 minutes preoperatively. Extracapsular cataract extraction using automated irrigation and aspiration extraction with intraocular lens placement was performed in a standard fashion in all patients. A viscoelastic substance (Healon) was used at the time of anterior capsulotomy and lens placement. The total volume of Healon used ranged from 0.2 to 0.5 ml, and averaged 0.3 ml.

Excess Healon was removed using an avit mode (anterior vitrectomy) for ten seconds, with the tip placed approximately in the mid pupil position. At the end of surgery, the randomized intracameral injection of either balanced salt solution or carbachol was given. Finally, a subconjunctival injection was administered consisting of 0.5 ml of gentamicin and 0.5 ml of betamethasone.

Intraocular pressures by applanation tonometry were measured preoperatively and at three, six, 12, 24, and 48 hours. The pupil size, anterior chamber cell and flare, and a clinical evaluation of overall ocular discomfort were also recorded.

Results

Table 1 lists the intraocular pressures obtained throughout the postoperative periods with their respective standard errors. The same data are graphically illustrated in the Figure. Intraocular pressures in the fellow eyes remained constant and were not statistically different preoperatively in either the control or the study groups.

Results of Student *t*-tests showed that eyes that received 0.5 ml of carbachol maintained significantly lower intraocular pressures throughout the 48-hour study period (Table 2). Eyes that received the 0.25- or 0.1-ml doses of carbachol also maintained significantly lower intraocular pressures through the first 24 postoperative hours.

Of the 13 patients receiving balanced salt solution, intraocular pressures exceeded 21 mm Hg in ten. Six patients had intraocular pressures greater than 30 mm Hg and two had pressure spikes greater than 40 mm Hg.

In the intracameral carbachol treatment groups, only two of 19 patients had intraocular pressure spikes greater than 21 mm Hg. Both of these patients received 0.1 ml of carbachol. One of these patients had an intraocular pressure of 24 mm Hg at 24 hours, with all other pressures well controlled. A second patient in this group had a pressure spike of 40 mm Hg at six hours and 34 mm Hg at 12 hours. All other pressures were below 21 mm Hg.

The effectiveness, duration of action, and potential toxicity of intracameral carbachol compared with acetylcholine for the induction of miosis during cataract surgery has been previously described.[3-5] In our treated patients, miosis was routinely seen at 24 hours and commonly seen at 48 hours. This miosis caused a pinhole effect, which was readily discernible on the first postoperative day by checking an unaided visual acuity. One could argue that the miosis and secondary pinhole effect would make it difficult to perform this study in a double-masked fashion.

The amount of cell and flare in the anterior chamber at the different postoperative times was assessed and recorded. These were rated subjectively on a scale of 1 through 4, with 4 representing the maximum amount of cell and

TABLE 1
AVERAGE (S.E.) POSTOPERATIVE INTRAOCULAR PRESSURES (mm Hg)

GROUP	PREOPERATIVE	3 HRS	6 HRS	12 HRS	24 HRS	48 HRS
Balanced salt solution, 0.5 ml (n = 6)	15.2 (1.0)	21.7 (2.2)	24.0 (2.3)	24.3 (3.4)	22.8 (3.0)	14.8 (2.2)
Balanced salt solution, 0.1 ml (n = 7)	15.9 (1.0)	27.4 (3.2)	27.9 (3.7)	25.0 (3.2)	22.6 (2.6)	NA*
Carbachol, 0.5 ml (n = 6)	12.8 (1.1)	4.7 (1.0)	5.3 (1.0)	8.0 (0.9)	9.2 (1.8)	4.2 (1.0)
Carbachol, 0.25 ml (n = 5)	14.6 (1.5)	7.4 (2.5)	6.8 (0.8)	7.2 (1.7)	11.8 (2.9)	9.5 (1.7)
Carbachol, 0.10 ml (n = 8)	14.6 (0.4)	7.6 (1.2)	12.4 (4.1)	14.5 (3.1)	15.3 (1.9)	12.7 (2.0)

*NA, not available.

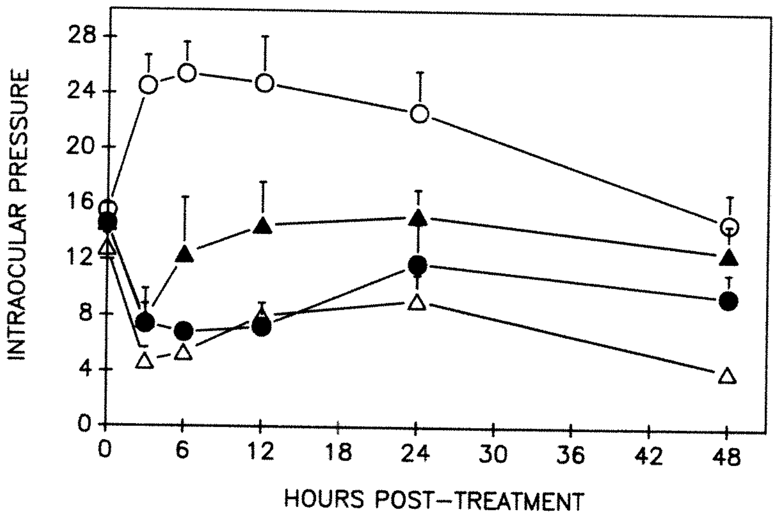

Figure (Linn and associates). Intraocular pressures of all patients treated with carbachol compared to all patients receiving balanced salt solution. Open circles, control groups; closed circles, 0.25 ml of carbachol; open triangles, 0.5 ml of carbachol; closed triangles, 0.1 ml of carbachol.

flare for any postoperative period. We did not demonstrate any difference in anterior chamber cell and flare in the perioperative period when comparing control and treated groups.

At each postoperative time period the patients were asked to rate the amount of pain. Pain was subjectively recorded on a scale of 1 through 10, with 1 through 3 considered mild, 4 through 6 moderate, and 7 through 10 severe. The maximum pain noted for any postoperative time period was collated. Of the control patients, one of 13 (8%) reported severe pain at some time in the postoperative course. However, five of 19 (26%) carbachol-treated patients reported severe pain at some time during the postoperative period. To evaluate the postoperative discomfort further, we retrospectively evaluated the number of patients who requested pain medication postoperatively. Four of 13 patients (30%) in the control groups requested pain medicines as compared to eight of 19 (42%) in the carbachol-treated groups. However, none of the patients reported persistent pain throughout the postoperative period. The pain invariably was transient and seen within the first 12 hours postoperatively. We found no relationship between the amount of carbachol injected and the subjective complaint of postoperative pain.

Discussion

Carbachol (carbamylcholine chloride) is a potent parasympathomimetic that has both muscarinic and nicotinic properties. Substitutions of the nitrogen-hydrogen-2 group to the basic acetylcholine molecule has made carbachol resistant to cholinesterase hydrolysis. Because the molecule carries a positive charge, topically applied carbachol penetrates the corneal epithelium poorly. Surfactants such as benzalkonium chloride are needed to increase corneal penetration. Carbachol is commonly used for both the topical treatment of glaucoma and for intraocular surgery to produce miosis.[6-8] Although carbachol may function through nu-

TABLE 2
P VALUES*

GROUPS	PREOPERATIVE	3 HRS	6 HRS	12 HRS	24 HRS	48 HRS
0.5 ml balanced salt solution vs 0.5 ml carbachol	NS	.0001	.001	.002	.003	.001
0.5 ml balanced salt solution vs 0.25 ml carbachol	NS	.002	.0001	.002	.03	NS
0.1 ml balanced salt solution vs 0.1 ml carbachol	NS	.0001	.02	.04	.04	NS

*NS, not significant.

merous mechanistic pathways, it is classically thought to have a double action, not only to stimulate the motor endplate of the effector muscle cells as all cholinesters do, but also partially to inhibit cholinesterase. Carbachol's duration of action is longer and on a weight-by-weight basis more potent than acetylcholine.

Our results showed that 0.5 ml of 0.01% carbachol was highly efficacious in controlling intraocular pressure through the 48th hour postoperatively. Both 0.25 and 0.1 ml of 0.01% carbachol were also efficacious at 24 hours. There were no patients with intraocular pressures greater than 21 mm Hg in either the 0.5- or the 0.25-ml carbachol-treated groups. In the 0.1-ml carbachol-treated group, two patients had an intraocular pressure spike greater than 21 mm Hg. The first patient had an intraocular pressure of 24 mm Hg at 24 hours. This same patient had intraocular pressures of 10 mm Hg or below at three, six, and 12 hours postoperatively. In the second patient, who had postoperative pressure spikes of 40 mm Hg at six hours and 34 mm Hg at 12 hours, 0.5 ml of Healon was used and miosis appeared to be less than that noted in the other carbachol-treated patients. The intraocular pressure spike in this patient could be explained in two ways. One, the 0.1-ml dose of carbachol is approaching the lower limit of the expected dose-response curve. Two, the small volume may not have been adequately injected into the anterior chamber or a washout may have occurred. Before the treated eyes were injected with carbachol at the end of surgery, intraocular pressure was returned to normal. The surgeon then trimmed and buried the knots where appropriate and checked the wound for leaks. Only when the eye was judged to have an adequate intraocular pressure without wound leak was the final injection of either balanced salt solution or carbachol given. A tuberculin syringe was used for the intracameral injection. When the surgical wound was opened and the 0.1 ml of carbachol injected, a certain amount of active agent may have washed out, thus resulting in less miosis and less pressure control.

This potential washout might be avoided by diluting the 0.01% carbachol by a factor of two and injecting 0.2 ml of solution. Because no statistical difference was shown between intraocular pressure in either the 0.5-or the 0.1-ml balanced salt solution control groups, further dilutions of the carbachol into a higher volume should not change its postoperative effect.

Intracameral carbachol is highly efficacious at blunting postoperative intraocular pressure increases. The duration of action for 0.5 ml of carbachol was at least 48 hours and for 0.25 and 0.1 ml, 24 hours. Additional studies using a lower concentration, that is, a higher volume of diluent, would enable one to define accurately the lower limit of the intracameral carbachol dose-response curve. We will perform a one-year follow-up examination on the treated patients to observe for any long-term side effects. Clinically, we recommend using 0.25 ml of carbachol at the end of surgery as an aid in controlling intraocular pressure increases after cataract extraction.

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Pseudoglaucomatous Physiologic Large Cups

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Using planimetric analysis of stereoscopic optic disk photographs, we studied 21 optic nerve heads of 11 subjects who shared the common feature of optic cups that were larger than the mean + 2 S.D. within the normal population. A comparison of these findings to those of 571 normal optic disks and 706 optic nerve heads in eyes with chronic primary open-angle glaucoma showed the following morphologic characteristics: (1) abnormally large optic disk area (mean ± S.D., 4.49 ± 0.56 mm²), (2) large cup/disk ratios with the horizontal ratio (0.78 ± 0.03) significantly ($P <$ .001) larger that the vertical (0.71 ± 0.03), (3) increased incidence of cilioretinal arteries, (4) normal neuroretinal rim area (2.06 ± 0.35 mm²), (5) normal neuroretinal rim configuration, inferiorly (0.43 ± 0.08 mm) broader ($P <$ .001, Wilcoxon test) than superiorly (0.33 ± 0.06 mm), smallest ($P <$ .0001) temporally (0.20 ± 0.04 mm), (6) normal form of zone alpha (irregular hypopigmentation and hyperpigmentation) of the parapapillary chorioretinal atrophy with its widest extension in the temporal horizontal area, (7) no zone beta (visible large choroidal vessels and sclera), (8) normal caliber of the parapapillary retinal vessels, and (9) normal parapillary retinal nerve fiber layer. These characteristics are helpful in the differentiation of primary and secondary large cups.

Cupping of the optic disk is a typical feature of glaucomatous optic nerve damage. Its extension has been estimated with the ratio of the cup to disk diameter.[1] There are, however, individuals with an abnormally high cup/disk ratio but no pathologic findings. We undertook this study to identify intrapapillary and juxtapapillary characteristics that may be helpful in the differentiation of glaucomatous eyes and normal eyes with high cup/disk ratios.

Accepted for publication Oct. 25, 1988.

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Subjects and Methods

We studied 21 optic disks of 11 subjects (five men and six women) that were part of a group of 620 normal optic disks that had been evaluated in a prospective study since 1986. These optic cups were considered large cups (Figs. 1 and 2) because they were larger than 2.12 mm², the mean + 2 S.D. of 457 normal optic cups ($0.72\ mm^2 + 2 \times 0.70\ mm^2 = 2.12\ mm^2$).[2] The mean ± S.D. age of the 11 subjects was 41.3 ± 20.3 years (range, 3 to 60 years) and refraction was −0.33 ± 0.95 diopters (range, −2.00 to +1.25 diopters). Severely myopic eyes with a myopic refraction of more than −8.00 diopters were excluded because of characteristically different morphologic optic disk features: the optic disk area in severely myopic eyes is inversely correlated to the refraction and reaches values up to 20 mm², the optic disk form is often obliquely oval, and myopic parapapillary chorioretinal atrophy is difficult to distinguish from glaucomatous parapapillary chorioretinal atrophy.[3] The subjects were recruited for this study through referrals by ophthalmologists because of high cup/disk ratios or through routine office visits. No subject had any ocular abnormalities other than high cup/disk ratios. The anterior chamber angle was open and the optic media were clear. No intraocular operations had been performed and there was no history of any intraocular disease. Intraocular pressure was less than 21 mm Hg in all cases, with at least three readings between 9 P.M. and 7 A.M. Visual field testing using Octopus programs 32-34 or G1 showed only an enlarged

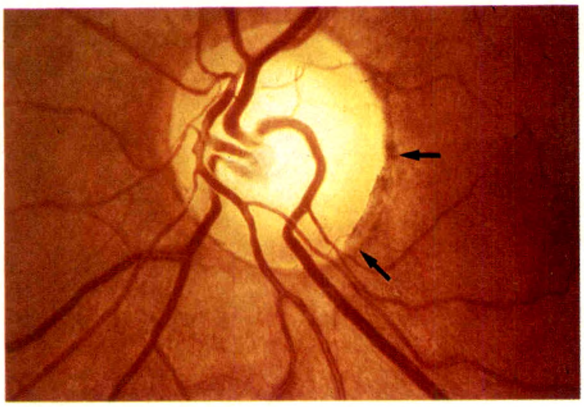

Fig. 1 (Jonas and associates). Primary large disk with pseudoglaucomatous but physiologic large cup. Optic disk: area, 4.80 mm^2; horizontal diameter, 2.35 mm; vertical diameter, 2.65 mm. Optic cup: area, 2.34 mm^2; horizontal diameter, 1.80 mm; vertical diameter, 1.76 mm. Horizontal cup/disk ratio, 0.77; vertical cup/disk ratio, 0.66; quotient of horizontal to vertical cup/disk ratio, 1.17. Neuroretinal rim: area, 2.46 mm^2; rim width temporally, 0.23 mm; nasally, 0.31 mm; superior disk pole, 0.43 mm; inferior disk pole, 0.46 mm. Area of zone alpha of the parapapillary chorioretinal atrophy (arrows) is 0.52 mm^2; there is no zone beta of the parapapillary chorioretinal atrophy (visible large choroidal vessels and visible sclera). Smallest part of the neuroretinal rim is in the temporohorizontal optic disk region.

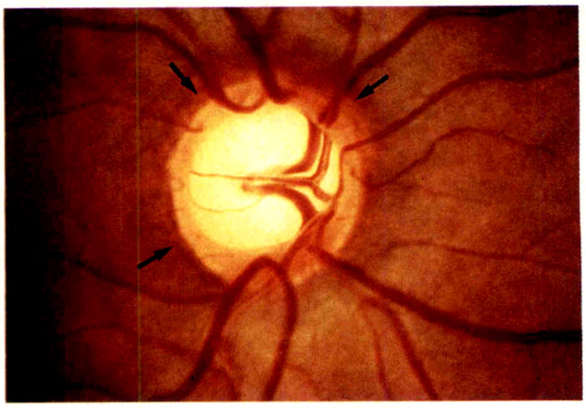

Fig. 2 (Jonas and associates). Primary large disk with pseudoglaucomatous but physiologic large cup. Optic disk: area, 4.23 mm^2; horizontal diameter, 2.24 mm; vertical diameter, 2.36 mm. Optic cup: area, 2.31 mm^2; horizontal diameter, 1.79 mm; vertical diameter, 1.63 mm. Horizontal cup/disk ratio, 0.80; vertical cup/disk ratio, 0.69; quotient of horizontal to vertical cup/disk ratio, 1.16. Neuroretinal rim: area, 1.92 mm^2; rim width temporally, 0.19 mm; nasally, 0.26 mm; superior disk pole, 0.29 mm; inferior disk pole, 0.44 mm. Area of zone alpha of the parapapillary chorioretinal atrophy (arrows) is 0.89 mm^2; there is no zone beta of the parapapillary chorioretinal atrophy (visible large choroidal vessels and visible sclera). Smallest part of the neuroretinal rim is in the temporohorizontal optic disk region.

blind spot. In some subjects, the retinal nerve fiber layer had been photographed and assessed according to the method described by Airaksinen and colleagues[4,5]; no pathologic findings had been detected. Results of neurologic, neuroradiologic, and medical examinations were normal.

We compared the 21 optic disks with physiologic large cups with 571 normal optic nerve heads of 350 subjects (196 men and 154 women) and with 706 optic disks of 378 patients (195 men and 183 women) with chronic primary open-angle glaucoma. Mean ± S.D. age in the normal control group was 43.5 ± 18.2 years (range, 3 to 81 years) and refraction measured an average of −0.20 ± 2.37 diopters (range, −7.88 to +7.50 diopters). Mean ± S.D. age of the glaucoma patients was 62.9 ± 13.2 years (range, 17 to 91 years) and refraction measured −0.27 ± 2.51 diopters (range, −7.50 to +12.75 diopters). Criteria for the diagnosis of chronic primary open-angle glaucoma were an open anterior chamber angle, intraocular pressure of more than 21 mm Hg or a history of increased intraocular pressure, glaucomatous visual field loss, and, in patients in whom retinal nerve fiber layer photography had been performed, alterations of the retinal nerve fiber layer.[4,5] Glaucomatous visual field loss included paracentral isolated or arcuate, relative or absolute scotomata, nasal steps of at least 10 degrees, and increased visual field indices on the Octopus program G1.

The optic disk photographs (15-degree color stereoscopic diapositives) had been taken with a telecentric fundus camera equipped with a stereoscopic separator. The diapositives were projected at a magnification of 15. The outlines of the papillary structures were plotted and analyzed planimetrically.

The intrapapillary and parapapillary areas were divided into four sectors: the inferotemporal and superotemporal sectors were right-angled and their middle lines were tilted 13 degrees temporal to the vertical optic disk axis. The sector on the temporal side and the sector on the nasal side covered the remaining area (nasally 64 degrees and temporally 116 degrees).

For the optic disk and optic cup we measured

area, horizontal, vertical, minimal, and maximal diameter, ratio of minimal to maximal diameter, and a form factor. The latter ranged from 0.0 to 1.0, with 1.0 indicating a perfect circle. The area of the neuroretinal rim was measured in the four sectors separately. Its total area was calculated as the difference of disk area minus cup area. The rim width was measured at 12 points, each 30 degrees apart. In the parapapillary region the peripapillary scleral ring of Elschnig[6] and the juxtapapillary chorioretinal atrophy were measured in the four sectors separately. Their total area was determined as a sum of the areas in the four sectors. The diameter of the superotemporal and inferotemporal retinal artery and vein were determined at the optic disk border.

The cup/disk ratios, the quotient of the horizontal to vertical cup/disk ratio, the ratio of the neuroretinal rim area of the inferotemporal disk sector divided by the rim area of the superotemporal disk sector, and the percentage of the rim areas in the four sectors on the total rim area were calculated.

As nonmorphometric characteristics, we evaluated the number of cilioretinal arteries and optic disk hemorrhages, the occurrence of a discrepancy between the area with pallor and the area with cupping, the location of the smallest part of the neuroretinal rim, the visibility of the parapillary retinal nerve fiber bundles on standard color optic disk diapositives, and the location of the widest extension of the parapapillary chorioretinal atrophy. The photographic magnification was corrected as described by Littmann.[7,8] Indirect evidence for the validity of this method was found when the 457 normal optic nerve heads, as determined intravitally using Littmann's method,[2] did not differ significantly in size and form from 107 optic nerve scleral canals that had been measured directly in human unfixed donor eyes.[9]

Definition of the intrapapillary and parapapillary structures

Intrapapillary—The optic disk was defined as the area inside the white peripapillary scleral ring of Elschnig. The optic cup was defined on the basis of contour, not pallor. Vessels were considered as part of the optic cup if there was no underlying neuroretinal rim tissue; otherwise they were considered to be part of the rim. This topographic definition of the intrapapillary optic disk structures has also been used by others.[10-19]

Parapapillary—The peripapillary scleral ring of Elschnig[6] was defined as the white, often circular, band surrounding the optic nerve head. It was frequently easier to detect on the temporal disk side. The juxtapapillary chorioretinal atrophy was divided into two zones: alpha and beta. Zone alpha was characterized by an irregular hypopigmentation and hyperpigmentation, and intimated thinning of the chorioretinal tissue layer. It was adjacent to the retina on its outer side and to zone beta, or the peripapillary scleral ring of Elschnig, on its inner side. Zone beta was characterized by marked atrophy of the retinal pigment epithelium and of the choriocapillaris, small gray fields on a white background, good visibility of the large choroidal vessels and sclera, thinning of the chorioretinal tissues, round bounds to the adjacent zone alpha on the peripheral side, and to the peripapillary scleral ring of Elschnig on the central side. If both zones were present, zone beta was always closer to the optic disk than zone alpha.

This definition of the intrapapillary and juxtapapillary structures was agreed upon at the meeting "Biomorphometry of the Optic Nerve" (held in Erlangen, West Germany, Jan. 23, 1988).[20]

Reproducibility—The intraobserver and interobserver variation coefficients were determined recently.[21] Photographs of ten randomly selected normal optic nerve heads were independently reevaluated ten times each by two investigators (G.C.G. and J.B.J.). The intraobserver and interobserver variation coefficients for optic disk and cup area were 0.01 and 0.03, respectively.

Results

Intrapapillary

Optic disk—The area of the optic disks with physiologic large cups measured 4.49 ± 0.56 mm^2 (mean ± S.D.), with a miminum of 3.63 mm^2 and a maximum of 5.54 mm^2. The optic nerve heads were significantly larger ($P < .00001$, Mann-Whitney test) than 457 normal optic disks (2.69 ± 0.70 mm^2) that had been measured previously.[2] Fifteen optic disks exceeded the morphometric limit of a large disk,[22] defined as being larger than the mean + 2 S.D. of normal optic disks ($2.69\ mm^2 + 2 \times 0.70\ mm^2 = 4.09\ mm^2$). According to the gaussian distribution curve of optic disk size,[2] only 2.28% are expected beyond this limit. The optic disk form

was slightly vertically oval: the mean vertical diameter (2.45 ± 0.20 mm) was similar to the maximal diameter (2.53 ± 0.18 mm), and it was about 6% larger than mean horizontal diameter (2.31 ± 0.16 mm), which was similar to the minimal diameter.

The disk area in the normal control and the glaucoma group was significantly smaller than that in the study group. No differences between the groups were found for the optic disk form (Table 1).

Optic cup—The optic cup area was, by definition, larger than 2.12 mm² and measured 2.44 ± 0.30 mm² (range, 2.13 to 3.07 mm²). The cup form was slightly horizontally oval, as indicated by the horizontal and vertical cup diameters, the ratio of minimal to maximal diameter, and the form factor.

TABLE 1
MORPHOMETRIC OPTIC DISK AND OPTIC CUP DATA (MEAN ± S.D.)

	STUDY GROUP (RANGE) (N = 21)	NORMAL GROUP (N = 571)	GLAUCOMATOUS GROUP (N = 706)
Optic disk			
area (mm²)	4.49 ± 0.56 (3.63–5.54)	2.69 ± 0.70	2.65 ± 0.60
Diameter (mm)			
Horizontal	2.31 ± 0.16 (2.10–2.61)	1.78 ± 0.25	1.76 ± 0.22
Vertical	2.45 ± 0.20 (2.16–2.91)	1.90 ± 0.27	1.90 ± 0.22
Minimal	2.28 ± 0.14 (1.99–2.47)	1.74 ± 0.23	1.72 ± 0.20
Maximal	2.53 ± 0.18 (2.25–2.91)	1.95 ± 0.27	1.95 ± 0.22
Minimum/maximum	0.90 ± 0.04 (0.82–0.96)	0.89 ± 0.05	0.89 ± 0.05
Form factor	0.98 ± 0.01 (0.94–0.99)	0.97 ± 0.03	0.98 ± 0.40
Optic cup			
area (mm²)	2.44 ± 0.30 (2.13–3.07)	0.73 ± 0.59	1.66 ± 0.80
Diameter (mm)			
Horizontal	1.80 ± 0.14 (1.62–2.08)	0.92 ± 0.48	1.35 ± 0.37
Vertical	1.73 ± 0.12 (1.58–1.97)	0.84 ± 0.47	1.45 ± 0.39
Minimal	1.67 ± 0.11 (1.50–1.89)	0.78 ± 0.44	1.31 ± 0.35
Maximal	1.87 ± 0.13 (1.68–2.11)	0.92 ± 0.50	1.54 ± 0.39
Minimum/maximum	0.90 ± 0.05 (0.81–0.96)	0.72 ± 0.30	0.85 ± 0.08
Form factor	0.98 ± 0.02 (0.91–0.99)	0.81 ± 0.34	0.96 ± 0.05

The cup area of the normal optic nerve heads was significantly smaller ($P < .0001$). The cups of the glaucomatous eyes were larger than those in the normal control group and smaller than those in the study group (Table 1).

Neuroretinal rim—The mean ± S.D. neuroretinal rim area was 2.06 ± 0.35 mm² (range, 1.50 to 2.76 mm²) (Table 2). It was not significantly different (Mann-Whitney test) from the mean neuroretinal rim area of normal optic nerve heads (1.97 ± 0.50 mm²).[2] It was significantly broadest at the inferior optic disk pole, followed by the superior disk pole, the nasal disk side, and finally the temporal disk region (Table 2). In all optic nerve heads the narrowest part of the neuroretinal rim was in the temporohorizontal sector. The same neuroretinal rim configuration has been found in normal optic nerve heads.[2] The rim area in the inferotemporal disk sector was significantly larger than in the superotemporal one; the ratio of the inferotemporal rim area divided by the superotemporal rim area was 1.21 ± 0.19 (range, 0.83 to 1.56). In two eyes the rim area of the inferotemporal disk sector was smaller than the rim of the superotemporal sector. In the glaucoma group the rim was significantly smaller ($P < .00001$, Mann-Whitney test) and had lost its characteristic configuration (Table 2).

Cup/disk ratios—The cup/disk ratios were larger horizontally (0.78 ± 0.03) than vertically (0.71 ± 0.03) and ranged from 0.66 to 0.82. In only one optic disk was the horizontal cup/disk ratio smaller than the vertical one. The ratio of horizontal to vertical cup/disk ratio was 1.11 ± 0.07 (range, 0.90 to 1.22). The cup/disk ratios in the normal control group were significantly smaller ($P < .00001$, Mann-Whitney test). No significant difference was found with the cup/disk ratios of the glaucoma group.

The quotient of the horizontal to vertical cup/disk ratio was significantly larger in the normal eyes and significantly smaller in the glaucoma group ($P < .0001$, Mann-Whitney test).

Parapapillary

Peripapillary scleral ring of Elschnig—The peripapillary scleral ring of Elschnig was broadest in the temporal horizontal sector and narrowest in the nasal sector. It was slightly larger than

TABLE 2
MORPHOMETRIC NEURORETINAL RIM DATA
(MEAN ± S.D.)*

AREA (MM^2)	STUDY GROUP (RANGE) (N = 21)	NORMAL GROUP (N = 571)	GLAUCOMATOUS GROUP (N = 706)
Total	2.06 ± 0.35 (1.50–2.76)	1.96 ± 0.65	0.99 ± 0.64
Sector A	0.26 ± 0.05 (0.17–0.33)	0.25 ± 0.10	0.12 ± 0.11
Sector B	0.51 ± 0.12 (0.34–0.82)	0.48 ± 0.17	0.25 ± 0.17
Sector C	0.61 ± 0.12 (0.44–0.92)	0.51 ± 0.18	0.24 ± 0.19
Sector D	0.68 ± 0.11 (0.54–1.00)	0.61 ± 0.22	0.38 ± 0.20
Sector C/B	1.21 ± 0.19 (0.83–1.56)	1.07 ± 0.14	0.99 ± 1.13
Position 1	0.30 ± 0.08 (0.20–0.52)	0.45 ± 0.13	0.19 ± 0.12
Position 2	0.24 ± 0.06 (0.15–0.36)	0.36 ± 0.13	0.17 ± 0.11
Position 3	0.20 ± 0.04 (0.13–0.27)	0.32 ± 0.13	0.14 ± 0.10
Position 4	0.26 ± 0.06 (0.17–0.37)	0.37 ± 0.14	0.16 ± 0.10
Position 5	0.36 ± 0.07 (0.23–0.52)	0.48 ± 0.13	0.18 ± 0.11
Position 6	0.43 ± 0.08 (0.26–0.59)	0.53 ± 0.13	0.21 ± 0.11
Position 7	0.40 ± 0.05 (0.32–0.59)	0.51 ± 0.13	0.25 ± 0.10
Position 8	0.34 ± 0.04 (0.27–0.44)	0.48 ± 0.13	0.25 ± 0.10
Position 9	0.31 ± 0.07 (0.22–0.54)	0.47 ± 0.13	0.26 ± 0.11
Position 10	0.33 ± 0.07 (0.21–0.55)	0.48 ± 0.13	0.27 ± 0.12
Position 11	0.33 ± 0.07 (0.20–0.55)	0.50 ± 0.14	0.26 ± 0.11
Position 12	0.33 ± 0.06 (0.24–0.44)	0.49 ± 0.14	0.23 ± 0.12

*The optic disk area was divided into four sectors according to the most frequent location of glaucomatous notches in the neuroretinal rim at about 13 degrees temporal to the vertical optic disk poles; sectors B (superotemporal) and C (inferotemporal) were right-angled and their middle lines were tilted 13 degrees temporal to the vertical optic disk axis. Sector A (temporohorizontal, 64 degrees) and sector D (nasal, 116 degrees) covered the remaining area. Position numbers: the rim width (mm) was measured every 30 degrees, in left eyes clockwise and in right eyes counterclockwise.

that in the normal control and the glaucoma groups.

Parapapillary chorioretinal atrophy—Zone alpha of the parapapillary chorioretinal atrophy was broadest and most frequently found in the temporohorizontal sector, followed by the inferotemporal sector, the superotemporal sector, and finally the nasal area (Table 3). It was larger than that found in normal eyes. It was not significantly different from zone alpha in the glaucoma group. In 20 of the 21 eyes, its maximal extension was in the temporohorizontal sector. Zone beta did not occur in any eye with a physiologic large cup, but it did occur in 437 of the 706 glaucomatous eyes (61.9%) (Table 3).

Parapapillary retinal vessel diameter—The parapapillary diameters of the retinal vessels were not significantly smaller or larger than those in the normal group, but they were significantly larger than those in glaucomatous eyes. The vessels of the inferotemporal arcade were larger than the vessels of the superotemporal arcade. Because of the small number of eyes with physiologic large cups, these differences were not significant (Table 4).

TABLE 3
MORPHOMETRIC DATA (MEAN ± S.D.) OF ZONE ALPHA AND ZONE BETA OF THE PARAPAPILLARY CHORIORETINAL ATROPHY

AREA (MM^2)	STUDY GROUP (RANGE) (N = 21)	NORMAL GROUP (N = 571)	GLAUCOMATOUS GROUP (N = 706)
Zone alpha			
Total	0.78 ± 0.23 (0.23–1.24)	0.47 ± 0.69	0.63 ± 0.47
Sector A	0.36 ± 0.24 (0.12–1.04)	0.23 ± 0.19	0.31 ± 0.24
Sector B	0.13 ± 0.10 (0.00–0.40)	0.07 ± 0.13	0.13 ± 0.16
Sector C	0.16 ± 0.12 (0.01–0.46)	0.12 ± 0.31	0.16 ± 0.15
Sector D	0.13 ± 0.13 (0.00–0.47)	0.05 ± 0.23	0.09 ± 0.16
Zone beta			
Total	0.00	0.11 ± 0.36	0.70 ± 1.06
Sector A	0.00	0.05 ± 0.14	0.21 ± 0.28
Sector B	0.00	0.02 ± 0.08	0.14 ± 0.26
Sector C	0.00	0.04 ± 0.13	0.19 ± 0.30
Sector D	0.00	0.01 ± 0.07	0.17 ± 0.36

TABLE 4
MEAN ± S.D. PARAPAPILLARY RETINAL VESSEL DIAMETER (MM) MEASURED AT THE OPTIC DISK BORDER

VESSEL	STUDY GROUP (RANGE) (N = 21)	NORMAL GROUP (N = 571)	GLAUCOMATOUS GROUP (N = 706)
Superotemporal artery	0.105 ± 0.017 (0.090–0.130)	0.103 ± 0.020	0.088 ± 0.022
Inferotemporal artery	0.110 ± 0.022 (0.080–0.130)	0.109 ± 0.020	0.092 ± 0.025
Superotemporal vein	0.143 ± 0.026 (0.120–0.180)	0.134 ± 0.026	0.124 ± 0.028
Inferotemporal vein	0.150 ± 0.024 (0.130–0.180)	0.141 ± 0.022	0.125 ± 0.026

Nonmorphometric parameters

Cilioretinal arteries were detected on the photographs of 11 optic disks (52.4%). In three optic nerve heads, two cilioretinal vessels were found. A discrepancy between the area with pallor and the area with cupping was not found in any optic disk with a physiologic large cup but was found in nine (1.6%) of the normal eyes and in 408 (57.8%) of the glaucomatous eyes. Optic disk hemorrhages were not detected in the eyes with physiologic large cups but were found in 26 eyes (3.7%) in the glaucoma group. The parapapillary retinal nerve fiber bundles were visible on the standard color optic disk diapositives in all eyes with physiologic large cups. Visibility was decreased in 31 (5.4%) of the normal and in 601 (85.1%) of the glaucomatous eyes.

Discussion

The cup/disk ratio has generally been used to describe and quantify normal and glaucomatous optic nerve heads.[1] The ratio, however, varies in normal eyes from 0.0 to 0.87.[2] Therefore, a value of 0.8 can be normal or can indicate advanced glaucomatous optic nerve damage. Our results showed other morphologic characteristics that can be used to differentiate glaucomatous from normal eyes with high cup/disk ratios.

The optic disk was significantly larger ($P < .00001$, Mann-Whitney test) in the study eyes than in the normal and the glaucomatous eyes (Table 1). In 15 eyes the optic disks were larger than 4.09 mm^2. They were called primary large disks because they exceeded the limit of a mean normal optic nerve head plus 2 S.D. ($2.69\ mm^2 + 2 \times 0.70 = 4.09\ mm^2$).[2] The occurrence of physiologic large cups in primary large disks is explained by the correlation between the optic disk and cup size: the larger the disk, the larger the cup.[2,19,23,24] The primary large disks can be differentiated from secondary large disks that occur in congenital glaucoma and in severely myopic eyes.[3]

The optic disk form was not significantly different between the normal and glaucomatous eyes and the eyes with physiologic large cups. In all three groups the optic disk was slightly vertically oval, with the vertical diameter being about 6% larger than the horizontal one (Table 1). Therefore, disk form is not a useful characteristic with which to distinguish between glaucomatous and normal eyes with large cups.

The neuroretinal rim area was not significantly different between the study eyes and normal optic disks, but it was significantly larger than that in the glaucomatous eyes (Table 2). The rim configuration was typical: the rim was significantly broadest ($P < .001$, Wilcoxon test) at the inferior disk pole, followed by the superior disk pole, the nasal disk side, and in the temporal disk region ($P < .0001$, Wilcoxon test) (Table 2). The smallest part of the neuroretinal rim in all eyes with physiologic large cups was in the temporohorizontal disk sector. The same neuroretinal rim form has been found in normal optic nerve heads.[2] It is an important morphologic feature that can be checked during ophthalmoscopy and does not depend on results of time-consuming optic disk morphometry. It is correlated with the visibility of the retinal nerve fiber bundles, which in normal eyes are more visible in the inferotemporal region than in the superotemporal area,[25] with the diameter of the parapapillary retinal vessels, which are larger in the inferotemporal arcade than in the superotemporal arcade (Table 4), and with the location of the foveola, which is 0.53 ± 0.34 mm inferior to the optic disk center.[25]

The cup/disk ratios were unusually high in the study eyes, and reached values of up to 0.82. In all but one optic nerve head, the horizontal cup/disk ratio was higher than the vertical one. This can be explained by the form of

the optic disk, cup, and neuroretinal rim: the disk is vertically oval, the cup is horizontally oval, and the neuroretinal rim as a complement is broader at the superior disk poles than in the horizontal disk regions.

The high cup/disk ratios in these abnormally large but otherwise normal optic nerve heads show that the cup/disk ratio has only a limited value in describing and quantifying glaucomatous optic nerve damage. The dependence of the cup/disk ratio on the total optic nerve head size prevents this feature from being a diagnostically useful unit of measure. The quotient of horizontal to vertical cup/disk ratio, however, is independent of the disk size. It is significantly larger in normal than in glaucomatous optic nerve heads. This feature might be more useful than the horizontal or vertical cup/disk ratios only.

No difference between groups was found in the peripapillary scleral ring of Elschnig. Its evaluation is not helpful for the morphometric optic disk evaluation.

The parapapillary chorioretinal atrophy was divided into zone alpha, characterized by irregular hypopigmentation and hyperpigmentation, and zone beta, which had visible large choroidal vessels and sclera. Zone alpha was widest and most frequently found in the temporohorizontal sector and smallest and most rare in the nasal parapapillary region. The widest extension was in the temporohorizontal sector in all but one eye. The same form but a smaller zone alpha was found in the normal eyes, whereas in the glaucomatous eyes the widest extension was more often in the inferotemporal or superotemporal sector.

Zone beta did not occur in any eye with a physiologic large cup. In the normal eyes it was significantly smaller ($P < .0001$) and less frequent than in the glaucomatous eyes (Table 3). Evaluation of the parapapillary chorioretinal atrophy is, therefore, useful to differentiate glaucomatous from normal eyes with high cup/disk ratios. The measurement of zone beta is helpful particularly because the differences in size and frequency between the eyes with physiologic large cups and the normal eyes on the one hand and the glaucomatous eyes on the other were greater for zone beta than for zone alpha.

The parapapillary retinal vessel diameter was not significantly different from the caliber in the normal eyes, but it was significantly larger ($P < .0001$, Mann-Whitney test) than that in the glaucoma group (Table 4). A small retinal vessel diameter can thus be taken as an indicator of optic nerve damage in the differentiation between normal and glaucomatous eyes.

The inferotemporal vessels were larger than the superotemporal ones; however, these differences were not significant for the study eyes probably because of the small number of cases (Table 4). It correlates with the configuration of the neuroretinal rim in that the vessels in the inferior disk region were significantly broader than those in the superior disk area, with the superior visibility of the retinal nerve fiber bundles in the inferotemporal arcade,[25] and with the location of the foveola inferior to the center of the optic disk.[25]

Cilioretinal arteries were more common in the study eyes (52.4%) than in the normal eyes (normal values have been reported to range from 12.5% to 39.6%[26-29]). The abnormally high frequency of cilioretinal vessels in eyes with physiologic large cups corresponds with the correlation between the optic disk and cup size and the number of the cilioretinal vessels in normal eyes: the larger the optic nerve head and the optic cup, the more cilioretinal vessels.[30] The number of the cilioretinal arteries can be used as an indicator of an abnormally large optic disk.

No discrepancy was found between the area with pallor and the area with cupping in any optic disk with a physiologic large cup. Such a discrepancy, however, was found in 57.8% of the glaucomatous optic disks. The specificity of this characteristic to differentiate between the eyes with physiologic large cups and the glaucoma eyes was thus 100%, its sensitivity 57.8%, and its predictive value 59%.

The visibility of the parapapillary retinal nerve fiber bundles was unremarkable in the eyes with physiologic large cups, and it was decreased in 85.1% of the glaucomatous eyes. The specificity of 100% and the sensitivity of 85.1% of this nonmorphometric characteristic underlines its clinical value in the differentiation of normal and glaucomatous eyes.

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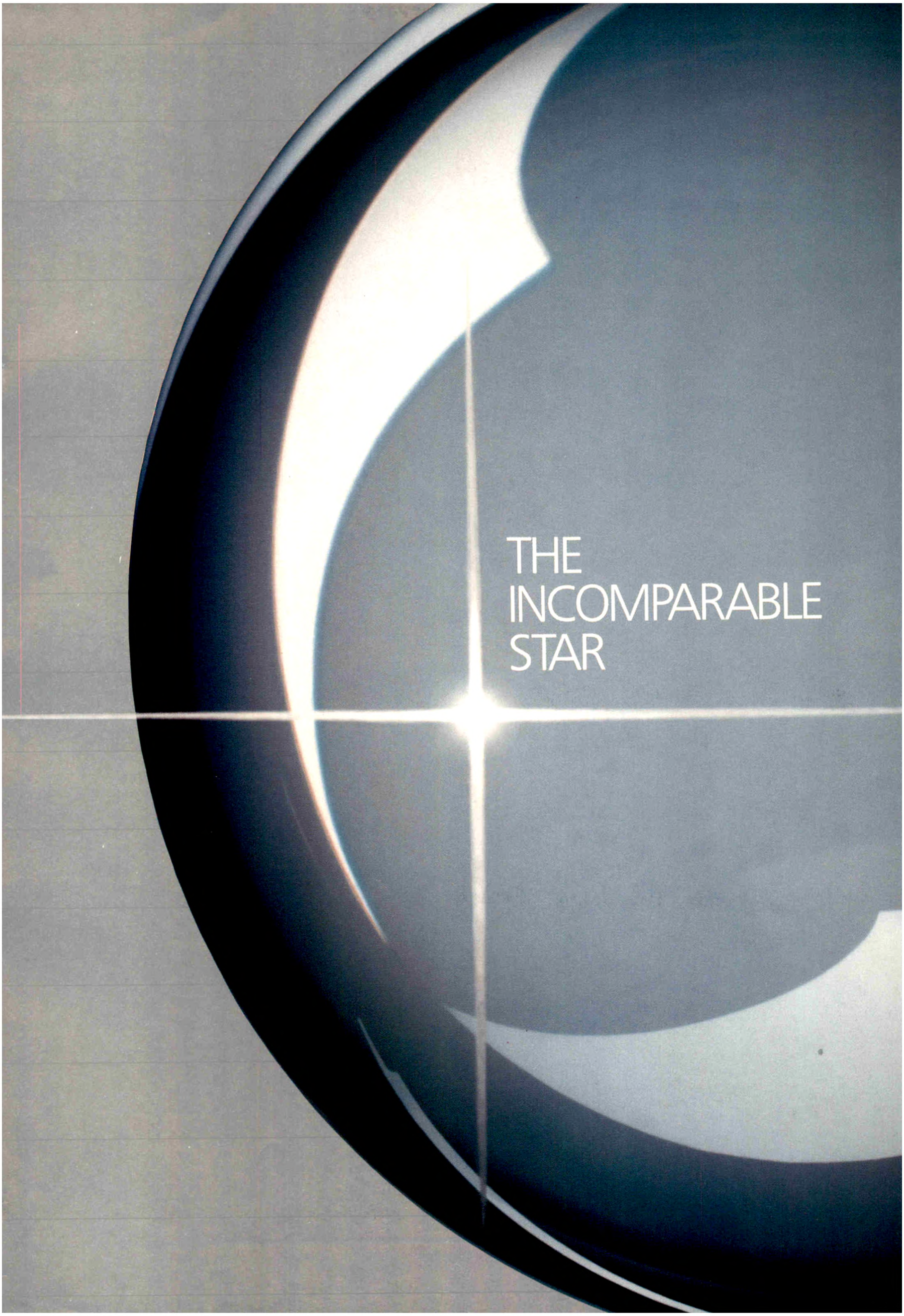
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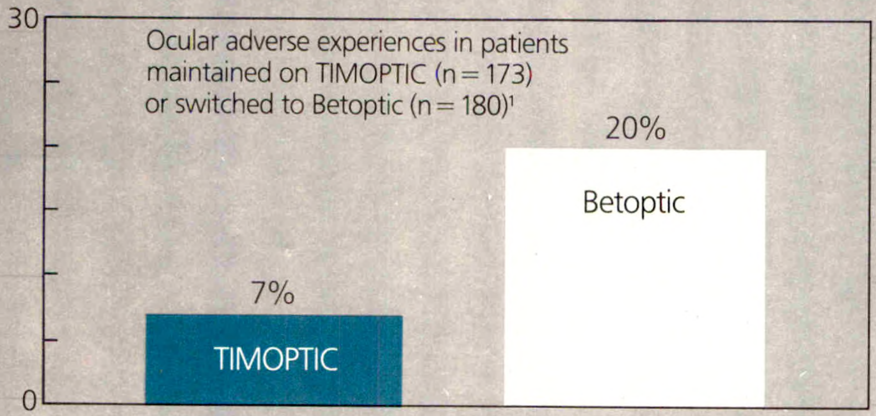

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[1]Data available upon request from Merck Sharp & Dohme, Professional Information, West Point, PA 19486-9989.

Five patients had a serious adverse experience during the study: four in the timolol treatment group and one in the betaxolol treatment group. Investigators considered four of these incidences either "definitely" not drug related or "probably" not drug related. One incident was considered "possibly" drug related; however, the patient continued in the study until relative Day 43.

Five patients were discontinued from the timolol treatment group due to an adverse experience. Ten patients were discontinued from the betaxolol treatment group due to an adverse experience.

Patients who are receiving a beta-adrenergic blocking agent orally and TIMOPTIC should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

TIMOPTIC is contraindicated in patients with bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease (see WARNINGS); sinus bradycardia; second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; and hypersensitivity to any component of this product.

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2. On the second day, discontinue the previously used agent and continue with TIMOPTIC in the affected eye(s) b.i.d.

How to transfer from several concomitantly administered antiglaucoma agents to TIMOPTIC:
1. If any agent is an ophthalmic beta-adrenergic blocker, discontinue before starting TIMOPTIC.
2. Continue the other agents being used, but add one drop of 0.25% TIMOPTIC to the affected eye(s) b.i.d.
3. On the following day, discontinue one of the other antiglaucoma agents.
4. The remaining antiglaucoma agents may be decreased or discontinued according to the patient's response to treatment.

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Dosage may be increased (from the 0.25% solution) by changing to one drop 0.5% TIMOPTIC twice a day in the affected eye(s). Dosages above one drop of 0.5% TIMOPTIC twice a day generally have not been shown to produce further reduction of IOP. If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to one drop once a day in the affected eye(s).

In patients with a history of severe cardiac disease, signs of cardiac failure should be watched for and pulse rates should be checked.

CONTRAINDICATIONS: TIMOPTIC is contraindicated in patients with bronchial asthma, a history of bronchial asthma, or severe chronic obstructive pulmonary disease (see WARNINGS); sinus bradycardia, second- and third-degree atrioventricular block; overt cardiac failure (see WARNINGS); cardiogenic shock; hypersensitivity to any component of this product.

WARNINGS: As with other topically applied ophthalmic drugs, this drug may be absorbed systemically.

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma and, rarely, death in association with cardiac failure, have been reported following administration of TIMOPTIC (see CONTRAINDICATIONS).

Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition by beta-adrenergic receptor blockade may precipitate more severe failure.

In Patients Without a History of Cardiac Failure: Continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, TIMOPTIC should be discontinued.

Obstructive Pulmonary Disease: PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (e.g., CHRONIC BRONCHITIS, EMPHYSEMA) OF MILD OR MODERATE SEVERITY, BRONCHOSPASTIC DISEASE OR HISTORY OF BRONCHOSPASTIC DISEASE (OTHER THAN BRONCHIAL ASTHMA OR HISTORY OF BRONCHIAL ASTHMA, IN WHICH 'TIMOPTIC' IS CONTRAINDICATED, see CONTRAINDICATIONS), SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS, INCLUDING 'TIMOPTIC'. However, if TIMOPTIC is necessary in such patients, then the drug should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery: The necessity or desirability of withdrawal of beta-adrenergic blocking agents prior to major surgery is controversial. Beta-adrenergic receptor blockade impairs the ability of the heart to respond to beta-adrenergically mediated reflex stimuli. This may augment the risk of general anesthesia in surgical procedures. Some patients receiving beta-adrenergic receptor blocking agents have been subject to protracted severe hypotension during anesthesia. Difficulty in restarting and maintaining the heartbeat has also been reported. For these reasons, in patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta-adrenergic receptor blocking agents.

If necessary during surgery, the effects of beta-adrenergic blocking agents may be reversed by sufficient doses of such agonists as isoproterenol, dopamine, dobutamine, or levarterenol.

Diabetes Mellitus: Beta-adrenergic blocking agents should be administered with caution to patients subject to spontaneous hypoglycemia or to diabetic patients (especially those with labile diabetes) who are receiving insulin or oral hypoglycemic agents. Beta-adrenergic receptor blocking agents may mask the signs and symptoms of acute hypoglycemia.

Thyrotoxicosis: Beta-adrenergic blocking agents may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. Patients suspected of developing thyrotoxicosis should be managed carefully to avoid abrupt withdrawal of beta-adrenergic blocking agents which might precipitate a thyroid storm.

PRECAUTIONS: *General:* Patients who are receiving a beta-adrenergic blocking agent orally and TIMOPTIC should be observed for a potential additive effect either on the intraocular pressure or on the known systemic effects of beta blockade.

Patients should not receive two topical ophthalmic beta-adrenergic blocking agents concurrently.

Because of potential effects of beta-adrenergic blocking agents relative to blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with TIMOPTIC, alternative therapy should be considered.

Muscle Weakness: Beta-adrenergic blockade has been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g., diplopia, ptosis, and generalized weakness). Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.

In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil with a miotic. TIMOPTIC has little or no effect on the pupil. When TIMOPTIC is used to reduce elevated intraocular pressure in angle-closure glaucoma, it should be used with a miotic an[d] not alone.

As with the use of other antiglaucoma drugs, diminished responsiveness to TIMOPTIC* (Timolol Maleat[e] MSD) after prolonged therapy has been reported in some patients. However, in one long-term study in whic[h] 96 patients have been followed for at least three years, no significant difference in mean intraocular pressu[re] has been observed after initial stabilization.

Drug Interactions: Although TIMOPTIC used alone has little or no effect on pupil size, mydriasis resulti[ng] from concomitant therapy with TIMOPTIC and epinephrine has been reported occasionally.

Close observation of the patient is recommended when a beta blocker is administered to patients receivi[ng] catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production [of] hypotension and/or marked bradycardia, which may produce vertigo, syncope, or postural hypotension.

Caution should be used in the coadministration of beta-adrenergic blocking agents, such as TIMOPTI[C] and oral or intravenous calcium antagonists, because of possible atrioventricular conduction disturbance[s], left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration shou[ld] be avoided.

The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may hav[e] additive effects in prolonging atrioventricular conduction time.

Animal Studies: No adverse ocular effects were observed in rabbits and dogs administered TIMOPTIC top[i]cally in studies lasting one and two years respectively.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year oral study of timolol maleate in rat[s] there was a statistically significant ($p < 0.05$) increase in the incidence of adrenal pheochromocytomas [in] male rats administered 300 times the maximum recommended human oral dose* (1 mg/kg/day). Simil[ar] differences were not observed in rats administered oral doses equivalent to 25 or 100 times the maximu[m] recommended human oral dose. In a lifetime oral study in mice, there were statistically significant ($p < 0.05$) increases in the incidence of benign and malignant pulmonary tumors and benign uterine polyps in fema[le] mice at 500 mg/kg/day, but not at 5 or 50 mg/kg/day. There was also a significant increase in mamma[ry] adenocarcinomas at the 500-mg/kg/day dose. This was associated with elevations in serum prolactin whic[h] occurred in female mice administered timolol at 500 mg/kg, but not at doses of 5 or 50 mg/kg/day. A[n] increased incidence of mammary adenocarcinomas in rodents has been associated with administration [of] several other therapeutic agents which elevate serum prolactin, but no correlation between serum prolact[in] levels and mammary tumors has been established in man. Furthermore, in adult human female subjects wh[o] received oral dosages up to 60 mg timolol maleate, the maximum recommended human oral dosage, there were no clinically meaningful changes in serum prolactin.

There was a statistically significant increase ($p < 0.05$) in the overall incidence of neoplasms in female mic[e] at the 500-mg/kg/day dosage level.

Timolol maleate was devoid of mutagenic potential when evaluated *in vivo* (mouse) in the micronucle[us] test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (u[p] to 100 µg/mL). In Ames tests, the highest concentrations of timolol employed, 5000 or 10,000 µg/plate were associated with statistically significant elevations ($p < 0.05$) of revertants observed with tester stra[in] TA100 (in seven replicate assays) but not in the remaining three strains. In the assays with tester stra[in] TA100, no consistent dose response relationship was observed, nor did the ratio of test to control revertan[ts] reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats showed no adverse effect on male or female fertility at doses up t[o] 150 times the maximum recommended human oral dose.

Pregnancy: Pregnancy Category C: Teratogenicity studies with timolol in mice and rabbits at doses up to 5[0] mg/kg/day (50 times the maximum recommended human oral dose) showed no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects o[n] postnatal development of offspring. Doses of 1000 mg/kg/day (1,000 times the maximum recommende[d] human oral dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 100 times the maximum recommende[d] human oral dose, in this case without apparent maternotoxicity. There are no adequate and well-controlle[d] studies in pregnant women. TIMOPTIC should be used during pregnancy only if the potential benefit justifie[s] the potential risk to the fetus.

Nursing Mothers: Because of the potential for serious adverse reactions from timolol in nursing infants, [a] decision should be made whether to discontinue nursing or to discontinue the drug, taking into account th[e] importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children have not been established by adequate and well-controlle[d] studies.

ADVERSE REACTIONS: TIMOPTIC Ophthalmic Solution is usually well tolerated. The following adverse reactions have been reported either in clinical trials of up to three years' duration prior to release in 1978 or sinc[e] the drug has been marketed.

BODY AS A WHOLE: Headache, asthenia, chest pain. CARDIOVASCULAR: Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, palpitation, cardiac arrest. DIGESTIVE: Nausea, diarrhea. NERVOUS SYSTEM/PSYCHIATRIC: Dizziness, depression, increase in signs and symptoms of myasthenia gravis, paresthesia. SKIN: Hypersensitivity, including localized and generalized rash, urticaria. RESPIRATORY: Bronchospasm (predominantly in patients with preexisting bronchospastic disease), respiratory failure, dyspnea, nasal congestion. ENDOCRINE: Maske[d] symptoms of hypoglycemia in insulin-dependent diabetics (see WARNINGS). SPECIAL SENSES: Signs an[d] symptoms of ocular irritation, including conjunctivitis, blepharitis, keratitis, blepharoptosis, decreased corneal sensitivity, visual disturbances, including refractive changes (due to withdrawal of miotic therapy i[n] some cases), diplopia, ptosis.

Causal Relationship Unknown: The following adverse effects have been reported, and a causal relationshi[p] to therapy with TIMOPTIC has not been established: *Body as a Whole:* Fatigue; *Cardiovascular:* Hypertension, pulmonary edema, worsening of angina pectoris; *Digestive:* Dyspepsia, anorexia, dry mouth; *Nervou[s] System/Psychiatric:* Behavioral changes including confusion, hallucinations, anxiety, disorientation, nervousness, somnolence, and other psychic disturbances; *Skin:* Alopecia; *Special Senses:* Aphakic cysto[id] macular edema; *Urogenital:* Retroperitoneal fibrosis, impotence.

The following additional adverse effects have been reported in clinical experience with oral timolol maleat[e] and may be considered potential effects of ophthalmic timolol maleate: *Body as a Whole:* Extremity pai[n], decreased exercise tolerance, weight loss; *Cardiovascular:* Edema, worsening of arterial insufficiency, Ray[n]aud's phenomenon, vasodilatation; *Digestive:* Gastrointestinal pain, hepatomegaly, vomiting; *Hematologi[c]:* Nonthrombocytopenic purpura; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Pruritus, skin irritatio[n], increased pigmentation, sweating, cold hands and feet; *Musculoskeletal:* Arthralgia, claudication; *Nervou[s] System/Psychiatric:* Vertigo, local weakness, decreased libido, nightmares, insomnia, diminished conce[n]tration; *Respiratory:* Rales, cough, bronchial obstruction; *Special Senses:* Tinnitus, dry eyes; *Urogenit[al]:* Urination difficulties.

Potential Adverse Effects: In addition, a variety of adverse effects have been reported with other bet[a-]adrenergic blocking agents and may be considered potential effects of ophthalmic timolol maleate: *Digestiv[e]:* Mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* Agranulocytosis, thrombocytopenic purpu[ra]; *Nervous System:* Reversible mental depression progressing to catatonia; an acute reversible syndrome cha[r]acterized by disorientation for time and place, short-term memory loss, emotional lability, slightly cloud[ed] sensorium, and decreased performance on neuropsychometrics; *Allergic:* Erythematous rash, fever co[m]bined with aching and sore throat, laryngospasm with respiratory distress; *Urogenital:* Peyronie's diseas[e].

There have been reports of a syndrome comprising psoriasiform skin rash, conjunctivitis sicca, otitis, a[nd] sclerosing serositis attributed to the beta-adrenergic receptor blocking agent practolol. This syndrome h[as] not been reported with timolol maleate.

HOW SUPPLIED: TIMOPTIC Ophthalmic Solution, 0.25% and TIMOPTIC Ophthalmic Solution, 0.5%. Bo[th] are available in 2.5-mL, 5-mL, 10-mL, and 15-mL plastic OCUMETER* ophthalmic dispensers with a co[n]trolled drop tip. **Also Available:** Preservative-free TIMOPTIC in OCUDOSE* (Dispenser) Sterile Ophthal[mic] Unit-Dose Dispenser (see separate Prescribing Information).

Storage: Protect from light. Store at room temperature.

*The maximum recommended single oral dose is 30 mg of timolol. One drop of TIMOPTIC 0.5% conta[ins] about 1/150 of this dose, which is about 0.2 mg.

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West Point, PA 19486

J8TM29(426)3

Large Optic Disks in the Marshallese Population

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On routine examination, asymptomatic patients from the Marshall Islands were noted to have large optic disks associated with high cup/disk ratios and normal intraocular pressure. We retrospectively analyzed color fundus photographs of 54 eyes and 22 eyes of 15 patients had optic disks greater than 2.10 mm, or megalopapilla. Of 36 patients with cup/disk ratios exceeding 0.6, 31 (86%) had visual acuities of better than or equal to 20/30. The optic nerve rim and disk areas varied directly as did disk and cup diameters. Three large disks with an 18-year photographic follow-up showed no change. Optic disk characteristics can vary widely among genetically isolated populations.

DURING ROUTINE ophthalmologic examination of a Micronesian population in the Republic of the Marshall Islands, a striking number of patients were noted to have large optic disks. These disks were associated with high cup/disk ratios without increased intraocular pressures, other disk anomalies, or any other ocular complaints.[1] This Pacific atoll population, which may be considered genetically isolated, demonstrates a large number of people with megalopapilla.

Fundus photographs were obtained on a group of patients noted to have high cup/disk ratios as well as on a randomly selected group of control patients. We performed a masked retrospective analysis of the fundus photographs in order to demonstrate that the optic disks that appeared on ophthalmoscopic examination to have high cup/disk ratios were actually larger than those optic disks judged clinically normal on ophthalmoscopy.

Subjects and Methods

The population examined consisted of 141 adults native to the Marshall Islands. Some had a history of radiation exposure in 1954, and it is to provide diagnosis and care of radiation-related illness that complete physical examinations are performed annually.[2] However, many unexposed patients are also examined. All examinees receive ophthalmologic evaluation, including slit-lamp examination, biennially. Visual acuities are measured with a Snellen chart at 20 feet. For this study there was no selection based on age, sex, previous radiation exposure, consanguinity, or ocular complaints or findings. The ocular examination was performed by an ophthalmologist (J.M.M.) who was part of the Brookhaven National Laboratory medical team. He completed a standardized examination form for each patient as well as performed the fundus photography. All patients thought to have abnormally large disks or high cup/disk ratios underwent fundus photography, as did many patients with normal disks who served as controls. Fundus photographs were taken in a total of 63 patients. The photographs were given to a masked observer (C.S.P.) for analysis.

Color slides of the optic nerve head taken with a fundus camera were projected onto the screen of a slide viewer. Using a ruler, measurements were made directly from the projected image. Black and white photographs of the optic disks of three patients were available from 1967, and measurements made directly from these photographs were compared to those of 1985.

Accepted for publication Oct. 14, 1988.
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This project was supported in part by the U.S. Deparment of Energy under Contract No. DE-AC02-76CH00016. Accordingly, the U.S. Government retains a nonexclusive, royalty-free license to publish or reproduce the published form of this contribution or allow others to do so for U.S. Government purposes.
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Measurements of the horizontal and vertical disk diameters were made carefully, excluding peripapillary halos and crescents. Horizontal and vertical cup diameters were estimated by color contrast taking into account changes in vessel direction at the cup edge as an indication of cup contour change where possible. The diameter of the largest vein on the disk edge was measured before it joined the central retinal vein. Finally, measurements of the superior, inferior, nasal, and temporal disk rim widths were made. Horizontal and vertical disk diameters were compared and then the two dimensions were combined to generate an average disk diameter which was used for further calculations and comparisons.

For 21 optic nerve heads, two to three slides of each nerve were available. In these cases, measurements were made from each slide and an average of the measurements was obtained.

In order to minimize the magnification or minification of the photographic image caused by the eyes' axial length, refractive power, and the camera optics, the actual disk and cup diameters were calculated by determining the ratio of the structure to that of a vein on the disk and multiplying by 125 μm, its actual size.[3] This method assumes that the vein on the disk will be subject to the same optical enhancement or reduction as the disk.

Actual diameter structure = 125 μm × measured structure/measured disk vein

Cup/disk ratios were calculated by dividing the cup diameter by that of the disk. To calculate the neural rim area, the horizontal and vertical disk and cup diameters were averaged and the areas for each were calculated using the following formula:

$$\text{Area of a circle} = \pi(\text{diameter}/2)^2$$

The cup area (C) was subtracted from the disk area (D) to yield the rim area (R).

The presence or absence of glaucomatous features such as disk asymmetry, vertical disk cupping, and notching of the neural rim were assessed.

Correlations between disk diameter, cup diameter, rim area, and cup/disk ratio vs history of radiation exposure, visual acuity, and intraocular pressure were studied.

Results

Acceptable photographs were available for 54 eyes of 36 patients. There were 15 men (42%) and 21 women (58%). They ranged in age from 30 to 67 years, with a mean ± S.D. age of 44.1 ± 11.3 years for the men and 43.5 ± 10.2 years for the women. Of the 36 patients, 19 (53%) had a history of radiation exposure. Only two pairs of subjects were known to be related. The first pair, a mother and a son, had relatively large disk diameters of 1.8 mm and 2.1 mm, respectively, in their right eyes. The mother had a cup/disk ratio of 0.5, whereas her son with a larger disk had a cup/disk ratio of 0.7. The second pair of related individuals were sisters. Each had disk diameters of 1.65 mm and cup/disk ratios of 0.4 in their left eyes. Information on the fellow eyes in both pairs of individuals was not available. Although there were similarities in disk size and cup/disk ratios between each of these related individuals, no firm conclusions concerning heredity can be drawn given such a small sample size.

The optic disk—Franceschetti and Bock[4] calculated the mean ± S.D. optic disk diameter of a normal Swiss population to be 1.62 ± 0.153 mm. In those eyes with oval disks, they averaged the vertical and horizontal measurements, as was done in this study. They reasoned that since only 0.26% of the observations in a normal distribution would be expected to exceed three standard deviations from the mean, which corresponded to 2.08 mm in their study, megalopapilla could be defined as a disk diameter greater than 2.08 mm.[5]

Because photographs were taken mainly of large optic disks with some normal disks for comparison, the distribution in our study would naturally be skewed. Therefore, a disk diameter greater than or equal to 2.1 mm was adopted from Franceschetti and Bock's study as the criterion for a large optic disk. The average disk diameter in this study population was 1.93 ± 0.28 mm (Fig. 1).

Of 54 eyes, 22 had optic disks with a diameter greater than or equal to 2.1 mm. Fifteen of 36 patients had large optic disks, the condition being bilateral in seven patients and unilateral in eight. Examples of large optic disks are shown in Figure 2.

Cup/disk ratio—In the Framingham Eye Study, the average cup/disk ratio was 0.28 ± 0.17 and two standard deviations above the

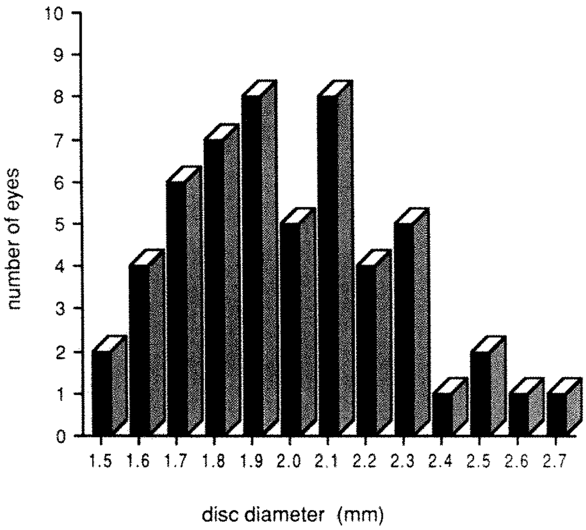

Fig. 1 (Maisel and associates). Disk diameter plotted against number of eyes. Quantitative analysis of patients selected for photographs demonstrates 22 eyes with megalopapilla with average disk diameters greater than or equal to 2.1 mm.

mean was equal to 0.62.[6] Because two or more standard deviations above the mean accounted for only 7.5% of their study population, 0.6 or more was accepted as the criterion for a large cup/disk ratio in our study.[5] This criterion is in agreement with Syndacker's work[7] in which he concluded that optic disks with physiologic cupping exceeding 0.66 occur so infrequently that it is to be considered pathologic until proven otherwise.

Such physiologic cupping as defined above was found in 20 of 22 eyes (91%) with large optic disks, but in only eight of 32 eyes (25%) with small disks. When cup vs disk diameter was plotted, the two variables were found to be linearly related (Fig. 3).

Rim area—When rim area was plotted against disk area, it was found that in this study population, rim and disk areas vary directly (Fig. 4).

Radiation exposure—Of the 36 patients, 19 had a history of accidental exposure to external whole-body radiation during atmospheric nuclear testing in 1954. Nine patients from the Rongelap atoll received an estimated 1.75 Gy (175 rad) and the ten patients from the island of Utirik received approximately 0.14 Gy (14 rad).[2]

Of the 36 patients in this study, 19 (a group different from the 19 above) had acceptable photographs of both eyes: 12 of these 19 had been exposed to radiation, five had not, and in two the data were not available. A comparison of the disk sizes in the 12 exposed and five nonexposed patients demonstrates that the two groups have relatively the same proportion of patients with large disks (Table 1).

Evidence of glaucoma—Features considered to be consistent with glaucomatous optic disk damage other than cupping, such as notching of the neural rim, disk asymmetry, vertical disk cupping, and increased intraocular pressure were investigated. Examination of the neural rim of the optic disk showed 360 degrees of pink neural tissue without notching in all cases. In the 19 patients for whom data were available on both eyes, two had asymmetric

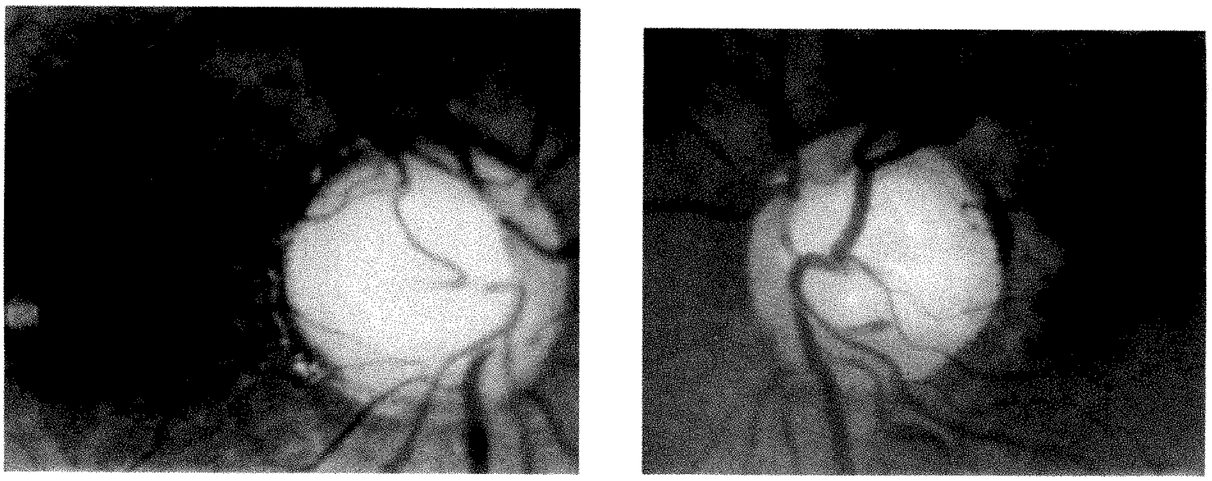

Fig. 2 (Maisel and associates). Example of bilateral megalopapilla. Left, Right disk diameter of 2.3 mm. Right, Left disk diameter of 2.2 mm.

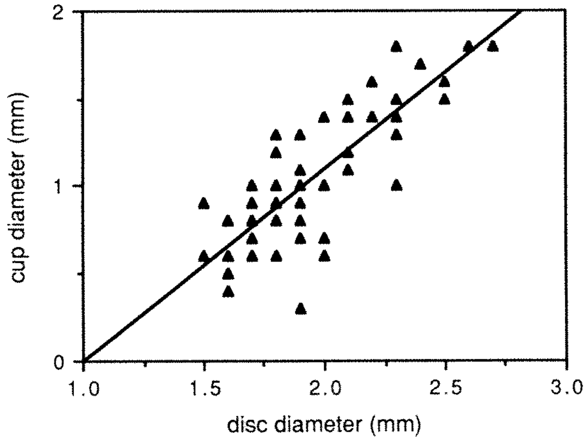

Fig. 3 (Maisel and associates). Cup diameter plotted against disk diameter showing that large disks tend to have large cups.

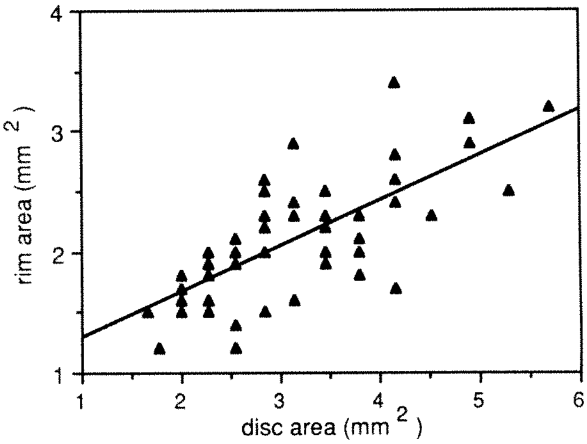

Fig. 4 (Maisel and associates). Rim area plotted against disk area showing that large disks tend to have greater rim area.

disks. These two patients had differences in their cup/disk ratios equal to 0.2, with no other stigmata of glaucoma. Disk asymmetry, that is, disks whose cup/disk ratios differ by more than 0.2, was found by Armaly to represent only 0.5% of the normal population.[8]

Vertical disk cupping where the vertical cup diameter exceeds that of the horizontal was found in 17 of 54 eyes. In each case, the vertical measurement did not exceed that of the horizontal by more than 0.01 mm, a difference which would probably go unnoticed when observed through an ophthalmoscope.

The average ± S.D. intraocular pressure was calculated after grouping the eyes into four categories. Eyes with large disks and large cups had an intraocular pressure of 11.8 ± 1.8 mm Hg; those with small disks and small cups, 11.4 ± 1.6 mm Hg; those with small disks and large cups, 11.5 ± 2.3 mm Hg; and those with large disks and small cups, 12.5 ± 2.5 mm Hg. There was no significant difference between the groups.

Visual acuity—Of the 36 patients, 31 (86%) had visual acuities better than or equal to 20/30 and 23 (64%) saw 20/20 or better. Of the five patients with visual acuities less than 20/30, three had reduced vision attributed to cataract. As a result of congenital nystagmus plus bilateral pigment mottling in the macula from previous toxoplasmosis, the fourth patient had a visual acuity of 20/50. The fifth patient had an uncorrected visual acuity of 20/200, which improved with pinhole to 20/40, in both eyes. However, no visual acuity was recorded on the chart following refraction with a −2.50 sphere.

Long-term follow-up—Optic disk photographs taken in 1967, 18 years before this study, were available for three patients (Table 2). There was essentially no change in either disk or cup diameters over the 18-year period.

Discussion

In this genetically isolated population in the Marshall Islands, 15 patients were found to

TABLE 1
RADIATION EXPOSURE AND OPTIC DISK SIZE

DISK SIZE (MM)	EXPOSED (N=12)	NONEXPOSED (N=5)
Bilateral >2.1	6	2
Bilateral <2.1	5	2
Unilateral >2.1	1	1

TABLE 2
COMPARISON OF OPTIC DISKS AFTER 18 YEARS OF FOLLOW-UP

	1967		1985	
PATIENT NO.	DISK DIAMETER (MM)	CUP/DISK RATIO	DISK DIAMETER (MM)	CUP/DISK RATIO
1	2.2	0.90	2.1	0.75
2	2.2	0.70	2.2	0.70
3	1.7	0.70	1.8	0.70

have optic disk diameters that fell beyond two standard deviations above the mean of a normal white population. In most cases, physiologic cups were also large, resulting in pale disks because of the increased visibility of the lamina cribrosa. Each case was associated with a full, sharp rim of healthy pink neural tissue without evidence of glaucomatous damage and with good visual acuity. The 18-year follow-up in three patients showed no change suggestive of an acquired, progressive process.

The definition of megalopapilla is based on the distribution of optic disk sizes in a normal white population, but may not be applicable to all racial groups. Neither the exact prevalence of megalopapilla nor the mean optic disk or cup diameters in the Marshall Island population could be calculated because fundus photographs were taken mainly of patients with large disks and high cup/disk ratios with several normal disks for comparison. The nonrandom nature of this study would skew the distribution of disk and cup sizes toward the larger end of the spectrum. However, the finding of 15 cases of megalopapilla, which is equal to the number previously reported, is certainly significant.[9] This is not without precedent. In a study of uric acid levels in the Marshallese, it was concluded that the observed increases in serum uric acid levels were not restricted to a subset of persons with hyperuricemia. Instead, the distribution of uric acid levels throughout the entire population tested was gaussian, suggesting a mean value and normal range of uric acid that is approximately 1.0 mg/dl higher than that found in the United States. Since "hyperuricemia" is common throughout the Pacific, it is possible that megalopapilla also occurs with increased prevalence in the Marshall Islands.[10]

Another question is whether radiation exposure plays a role in these differences. In our study of megalopapilla, the small sample size precludes drawing conclusions based on statistical significance; however, since both exposed and nonexposed groups have relatively the same proportion of patients with large disks, it is unlikely that radiation exposure was a factor contributing to the formation of such. Additionally, the presence of a unilaterally large disk cannot easily be explained by whole-body radiation exposure.

The effect of age and sex on disk and cup size must also be addressed. Although most authors agree that the cup size probably does not vary appreciably with sex, there is some controversy as to whether it increases with age.[7,8] Two studies have found no change in cup size with increasing age,[11,12] whereas the Framingham Eye Study,[6] Pickard,[13] and Carpel and Engstrom[14] all found a slight increase in cup size with age. However, because age did not cause the cup/disk ratios to exceed 0.6 in these last three studies, we could not attribute our 20 cases (out of 54) of cup/disk ratios greater than 0.6 to age alone, if at all. For these reasons, the effect of age and sex on cup and disk sizes was not considered to be significant for this study.

Another interesting finding concerned the rim area. A study by Teal, Marin, and McCulloch[15] showed that although cup area increased with disk area, rim area remained constant, suggesting that in large disks, cups enlarged so as to keep the rim area and hence the amount of neural tissue the same from person to person. In contrast, our study showed that as disk and cup area increased, rim area increased as well. Although cup area increased with disk area enough to raise the cup/disk ratio, disk size seemed to be increased out of proportion to the physiologic cup, yielding a larger rim area than expected. Recent work[11,16] confirms our findings that disk and rim areas vary directly. Whether this larger rim area results from an increase in neural tissue or an increase in extraneuronal supporting tissue is uncertain.

In 1985 a study showed that blacks tend to have significantly larger cup/disk ratios than whites (0.35 mm for blacks and 0.24 mm for whites).[17] However, the investigators did not evaluate the disk size or rim area. It would be of interest to know whether physiologic cupping in blacks is associated with larger disks and if these disks contain a greater amount of neural or extraneuronal tissue. Conversely, disk size may not vary at all from that of the white population, thus leading to a situation where there is a smaller but adequate amount of neural or extraneuronal tissue. In either case, the amount of neural tissue becomes important when considering neuronal reserve under pathologic conditions such as glaucoma or compressive mass lesions that lead to optic atrophy.

Racial differences in disk and cup sizes are consistent with both Armaly's[8] and Bengtsson's[18] studies, which showed that cup and disk sizes are genetically determined. Although there were similarities in disk size and cup/disk ratios between two pairs of related individuals in this study, no firm conclusions

concerning heredity could be drawn. However, taken as a whole, within this genetically isolated population, it is not surprising to have found optic disk sizes and cup/disk ratios that are different from our usual white reference population.

Faced with a pale disk accompanied by a large cup/disk ratio, other signs and symptoms indicative of an optic disk abnormality are usually searched for. It is reasonable from this study to conclude that in addition to signs and symptoms such as decreasing visual acuity, visual field defects, pupil abnormalities, increased intraocular pressure, poor color vision, and defects in the peripapillary nerve fiber layer and the neural rim, one should also take into account the racial or ethnic background of the patient before determining that the disk is abnormal. Furthermore, given the variability in optic disk size, measurements of rim area may prove more useful when assessing neuronal loss than measurements of the cup/disk ratio.

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OPHTHALMIC MINIATURE

He stood, slightly stooped, his head inclined to catch whatever Mrs. Hobhouse next said to him, but looking away half right, so that Sarah saw only his eye-patch profile. Was a black patch, on its own, expressive? Sarah thought that it was. Seen by itself, thus, it looked like the round bulging eye of a nocturnal creature abroad in sunlight, staring myopically, alerted by some unexpected but familiar sound of which it awaited judgement of the source . . .

Paul Scott, *The Day of the Scorpion*. Book II *The Raj Quartet*
New York, Avon Books

Punctal Occlusion and Topical Medications for Glaucoma

Timothy C. Huang, M.D., and David A. Lee, M.D.

We studied the effects of punctal occlusion on the intraocular pressures of patients treated with topical medications for glaucoma. Silicone punctal plugs were used to occlude the inferior punctum of one eye in each of 19 patients treated with identical antiglaucoma eyedrops in both eyes. The intraocular pressures before and after punctal occlusion were compared. The eyes with the punctal plugs showed a statistically significant ($P < .0001$) decrease in pressure of 1.32 mm Hg after punctal occlusion when compared to that of the fellow control unplugged eyes. The intraocular pressures in the plugged eyes decreased an average of 1.82 mm Hg after punctal occlusion when compared to before punctal occlusion ($P = .001$). The intraocular pressure in the unplugged control eyes did not change significantly after punctal occlusion of the fellow treated eye.

Most topical ophthalmic medications with intraocular sites of action penetrate the eye through the cornea, conjunctiva, or sclera. The amount of medication absorbed is influenced by the amount of contact time between the medication and the ocular surfaces. Most of an eyedrop is lost to drainage within 15 to 30 seconds after instillation, which includes rapid drainage of 80% or more of the volume through the nasolacrimal system.[1] Inhibition of this rapid drainage may lengthen the contact time of the medication with the eye and increase its absorption and efficacy.

Inhibition of drainage through the nasolacrimal system may be achieved by manual occlusion with a fingertip, by placing plastic or collagen plugs into the puncta, or by permanently closing the puncta with cautery or laser. Zimmerman and Ziegler[2] have advocated nasolacrimal occlusion with fingertip pressure as a means of increasing ocular absorption of topical ocular medications. Many patients, however, are unable to practice proper manual nasolacrimal occlusion. We studied the effects of occlusion of the nasolacrimal system by using removable silicone punctal plugs on the ocular hypotensive action of topical antiglaucoma medications.

Material and Methods

Patients from the Glaucoma Service were selected for this study. Selection criteria included bilateral glaucoma or ocular hypertension with intraocular pressures controlled on glaucoma medication regimens that included one or more topical eyedrops. Both eyes of each patient were treated with identical types and dosages of medications. Exclusion criteria included past or current obstruction of the nasolacrimal system, and unwillingness or inability of the patient to give informed consent for the study.

After the nature of the study was fully explained and informed consent was obtained, a primary dye test (Jones I test) for nasolacrimal patency was performed. If no dye was recovered by this method from either side, it was assumed that the patient had a defect in the nasolacrimal system and was excluded from the study. If dye was recovered from both sides, a punctum plug was inserted into the inferior punctum of one eye. The eye in which the plug was inserted alternated between the two eyes of each subject entering the study. The fellow eye, which was not occluded, served as a control. The patients were instructed to continue their current regimen of glaucoma medications as usual. After placement of the plugs and waiting at least two days to allow equilibration to the plugs, each patient returned for three follow-up examinations on three different

Accepted for publication Nov. 22, 1988.
From the Jules Stein Eye Institute, Department of Ophthalmology, University of California at Los Angeles, Los Angeles. This study was supported by grant EY07701, the Elsie B. Ballantyne Fund, Research to Prevent Blindness, Inc., and the Lucille Simon Glaucoma Research Fund.
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days. The times of day of the follow-up examinations were chosen to approximate those of pressure measurements that had been taken before plug placement. During these follow-up visits the intraocular pressure of both eyes were measured in a masked fashion using a Goldmann applanation tonometer and recorded along with the time of day. These measurements were performed before further examination of the eye to prevent awareness of which eye had been plugged and thus minimize bias in the pressure measurements. A slit-lamp examination was then performed to look for changes on the external ocular surfaces and in the anterior segment. The patients were monitored for side effects and complications related to the punctum plugs or to the eyedrops.

The one-sample t-test was used to compare the three intraocular pressure readings taken after plug placement, with the most recent three or more measurements taken during clinic visits before plug placement without intervening changes in the medical regimen. Regression analysis was used to evaluate diurnal trends in the intraocular pressure of the plugged eyes, the intraocular pressure of control eyes, and the difference in intraocular pressures between the paired eyes. Regression analysis was also used to study the differences in intraocular pressure before and after punctal occlusion among patients using one, two, or three different classes of topical antiglaucoma medications (beta-blockers, miotics, and epinephrine compounds). $P \leq .01$ was considered significant.

Results

Nineteen patients completed the study (Table 1). There were 13 women and six men. The average age was 67 years (range, 49 to 85 years). Fifteen of the patients had chronic open-angle glaucoma, two had combined mechanism glaucoma and patent peripheral iridotomies in both eyes, one had low-tension glaucoma, and one had ocular hypertension. Four patients were using only one glaucoma eyedrop; three were using two different types of eyedrops; and 12 were using three types of eyedrops, six of whom also took an oral carbonic anhydrase inhibitor. Seven patients had undergone laser treatments or surgery for glaucoma. These procedures were all performed more than six months before the study; all patients had stable glaucoma controlled with eyedrops. Ten patients had the right lower punctum occluded and nine had the left lower punctum occluded.

Mean ± S.E. intraocular pressure readings of all eyes were 16.96 ± 0.72 mm Hg before and 15.14 ± 0.70 mm Hg after punctal plug placement (Table 2). Intraocular pressure readings of all fellow eyes were 16.57 ± 0.78 mm Hg before and 16.07 ± 0.84 mm Hg after plug placement. Analysis of only the eyes with occluded puncta showed an average decrease in intraocular pressure of 1.82 mm Hg after punctal occlusion, which was statistically significant ($P = .001$) (Table 3). Comparison of the unplugged eyes alone showed no statistical change in the intraocular pressures before and after occlusion of the fellow eye ($P = .25$). Comparison of the mean differences in intraocular pressure between the plugged eye and the control fellow eye of each patient before occlusion with those differences after occlusion showed that there was an average decrease of 1.32 mm Hg after punctal occlusion. This was statistically highly significant ($P < .0001$).

Of the 57 pressure readings taken after punctal occlusion, 49 were taken at a time of day that was matched to within two hours of a corresponding measurement before occlusion. Two of the readings were between two and four hours from the before-occlusion readings. In six of the readings after occlusion, the exact time of day of the corresponding measurements before occlusion had not been recorded; however, it could be ascertained whether the patient had been seen in the morning or afternoon, and thus the timing of the measurement after occlusion was matched to either the morning or afternoon, accordingly.

Comparison of the mean differences in intraocular pressure before and after punctal occlusion among the patients using one, two, or three classes of topical antiglaucoma medications showed no statistically significant differences between the three groups. There was no significant correlation between the decrease in intraocular pressure and the number of different glaucoma medications the patient used.

Each patient was followed up for three examinations on three different days after plug placement. The length of follow-up averaged 13.8 days (range, seven to 34 days). During the follow-up period, seven patients experienced adverse reactions to the plugs, none of which were serious. Four patients complained of irritation of the eye for two days after placement, after which the discomfort abated. Two patients complained of persistent, mild, occasional itch-

TABLE 1
PATIENT CHARACTERISTICS

PATIENT NO., AGE (YRS), SEX	DIAGNOSIS	MEDICATIONS*	PREVIOUS LASER OR SURGICAL TREATMENT
1, 80, F	Chronic open-angle glaucoma	3A	None
2, 60, M	Low-tension glaucoma	1A	None
3, 65, F	Chronic open-angle glaucoma	2B	None
4, 54, M	Chronic open-angle glaucoma	1C	None
5, 65, F	Chronic open-angle glaucoma	3B	Argon laser trabeculoplasty in both eyes
6, 49, M	Chronic open-angle glaucoma	3B	None
7, 79, F	Chronic open-angle glaucoma	3A	Argon laser trabeculoplasty in both eyes
8, 65, M	Chronic open-angle glaucoma	3C	None
9, 61, F	Combined mechanism glaucoma	2A	Argon laser peripheral iridotomy in both eyes
10, 57, M	Chronic open-angle glaucoma	3B	None
11, 68, F	Chronic open-angle glaucoma	3B	Argon laser trabeculoplasty in both eyes
12, 58, M	Chronic open-angle glaucoma	3A	Argon laser trabeculoplasty in right eye, filtering surgery in right eye
13, 82, F	Chronic open-angle glaucoma	2A	None
14, 85, F	Chronic open-angle glaucoma	1B	None
15, 71, F	Chronic open-angle glaucoma	3B	None
16, 72, F	Chronic open-angle glaucoma	3A	None
17, 60, F	Chronic open-angle glaucoma	3A	Filtering surgery in the right eye
18, 69, F	Combined mechanism glaucoma	3B	Argon laser peripheral iridotomy in both eyes, argon laser trabeculoplasty in right eye
19, 75, F	Ocular hypertension	1A	None

*Medication regimen for glaucoma: 1A = beta-blocker only; 1B = miotic only; 1C = epinephrine compound only; 2A = beta-blocker and miotic; 2B = beta-blocker and epinephrine compound; 3A = beta-blocker, miotics, and epinephrine compound; 3B = beta-blocker, miotics, epinephrine compounds, and oral carbonic anhydrase inhibitor; 3C = beta-blocker, pilocarpine, and echothiophate.

TABLE 2
MEAN INTRAOCULAR PRESSURES (MM HG)*

PATIENT NO.	EYE WITH PUNCTUM PLUGGED	BEFORE PLACEMENT OF PLUG		AFTER PLACEMENT OF PLUG	
		PLUGGED EYE	FELLOW EYE	PLUGGED EYE	FELLOW EYE
1	R.E.	18.5	20.5	13.7	18.7
2	L.E.	11.2	10.5	9.0	8.7
3	R.E.	25.0	25.3	22.3	25.7
4	L.E.	14.8	13.0	15.7	14.7
5	R.E.	16.8	15.2	14.7	14.0
6	L.E.	14.8	14.2	10.3	11.0
7	R.E.	21.2	18.0	19.0	17.7
8	L.E.	17.7	17.7	16.0	17.3
9	R.E.	17.8	17.2	13.3	13.0
10	L.E.	19.0	21.0	17.7	19.0
11	R.E.	13.5	14.2	15.0	17.0
12	L.E.	15.2	13.5	15.0	13.7
13	R.E.	14.6	15.2	14.7	16.0
14	L.E.	20.2	19.8	17.0	15.0
15	R.E.	17.0	16.3	11.3	13.3
16	L.E.	17.2	16.4	16.3	15.7
17	R.E.	17.4	16.8	15.7	17.7
18	L.E.	13.5	14.0	14.0	14.7
19	R.E.	16.8	16.5	17.3	18.7

*All measurements made by applanation tonometry.

TABLE 3
MEAN ± S.E. INTRAOCULAR PRESSURE (MM HG)

EYES	BEFORE PLACEMENT OF PLUG	AFTER PLACEMENT OF PLUG	CHANGE IN PRESSURE FROM BEFORE TO AFTER PLACEMENT OF PLUG	P VALUE
Plugged eyes	16.96 ± 0.72	15.14 ± 0.70	decrease 1.82 ± 0.46	.001
Unplugged eyes	16.57 ± 0.78	16.07 ± 0.84	decrease 0.50 ± 0.42	.25
Difference in pressure (plugged eye − unplugged eye)	0.39 ± 0.29	−0.93 ± 0.36	decrease 1.32 ± 0.25	<.0001

ing, but one of the two had preexisting chronic blepharitis. One patient complained of bothersome persistent epiphora of the occluded eye which necessitated wiping her eye several times a day. In one patient the plug extruded just hours before she came in for her final follow-up visit when she rubbed her eyes. No evidence of infection, persistent conjunctivitis, or corneal epitheliopathy was noted in any of the patients.

Discussion

This study suggests that occlusion of the lacrimal puncta may result in an increased efficacy of antiglaucoma eyedrops, as shown by a decrease in intraocular pressure. The mechanism responsible for this increased efficacy is probably that the punctal plugs inhibit drainage of the eyedrops through the nasolacrimal system, thus keeping the medication in contact with the ocular surfaces for a longer time. Because of this increased contact time, more of the medication is absorbed into the eye, resulting in increased efficacy. Our results are consistent with those of Zimmerman and associates[3] who showed that nasolacrimal occlusion increases intraocular absorption of topically applied fluorescein.

The decrease in intraocular pressure, although highly statistically significant, was less than 2 mm Hg. Therefore, we cannot determine from this study whether the decrease in intraocular pressure was clinically significant. We chose to occlude only the lower punctum, leaving the upper punctum patent, to avoid inducing excessive epiphora in our patients. Perhaps if both puncta had been occluded, the decrease in intraocular pressure would have been even greater. However, the incidence of epiphora also might have increased.

The punctal plugs were generally well tolerated by most patients. The two patients who reported mild, occasional itching showed no objective signs of changes on their external ocular surfaces. These two patients tolerated the mild ocular irritation without difficulty. The plug extruded in only one of the 19 patients (5.3%). In this patient, the plug could be placed only half-way into the punctum, and it extruded nine days after placement. This incidence of extrusion is lower than the 28% (nine of 32 eyes)[4] and 22% (three of 14 eyes)[5] reported previously in studies using similar plugs. Subsequent to our study, the manufacturer of the silicone plugs used in this study (Eagle Vision, Inc.) developed plugs shorter in overall length and shorter in the height of the dome that remains exposed after plug placement. The use of these newer plugs may decrease ocular irritation and extrusion. Only one of our 19 patients (5.3%) reported epiphora with just the lower punctum occluded. Willis and associates[5] reported a series of 18 patients with dry eyes who underwent occlusion of all four puncta with removable punctal plugs. Three of their patients (17%) complained of epiphora. Only one of our patients (5.3%), the one who experienced epiphora, had an adverse effect that was significant enough to contraindicate plug placement.

Noncompliance in the treatment of glaucoma has been called a "leading cause of glaucoma blindness."[6] Kass and associates showed that patients actually administered only 76% of their prescribed doses of pilocarpine[7] and only 83% of their prescribed doses of a beta-blocker.[8] It is likely that some patients would be even more noncompliant in practicing proper manual punctal occlusion for five minutes after instilling each eyedrop since it requires even more effort than instilling eyedrops. Occlusion of the puncta with punctal plugs may be a simple method of maximizing the effects of topical medications in these patients.

Another potential benefit of punctal occlusion is the reduction of systemic absorption of topical medications, which may result in fewer

systemic side effects. Zimmerman and associates[3] showed that nasolacrimal occlusion reduced the amount of systemic absorption of topical timolol maleate by more than 60%. In our series no patient reported any systemic side effects attributable to their eyedrops before or after plug placement. This may be because we selected patients who had been controlled with the same medications for an extended period of time. Patients who experienced significant side effects would have required modifications of their medication regimen and thus would not have been included in our study.

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OPHTHALMIC MINIATURE

No one knew exactly when she had begun to lose her sight. Even in her later years, when she could no longer get out of bed, it seemed that she was simply defeated by decrepitude, but no one discovered that she was blind. She had noticed it before the birth of José Arcadio. At first she thought it was a matter of passing debility and she secretly took marrow syrup and put honey on her eyes, but quite soon she began to realize that she was irrevocably sinking into the darkness, to a point where she never had a clear notion of the invention of the electric light, for when they put in the first bulbs she was only able to perceive the glow.

Gabriel Garcia Marquez, *100 Years of Solitude*
New York, Avon Books, 1971, p. 231

Acute Closed-Angle Glaucoma After Arteriovenous Fistulas

Stuart Fourman, M.D.

Unilateral secondary acute closed-angle glaucoma was associated with a ciliochoroidal detachment in two patients. One patient, aged 17 years, had an orbital arteriovenous fistula. The other patient, aged 73 years, had a dural arteriovenous fistula that originated from branches of the right internal maxillary artery. In each patient there was increased intraocular pressure, a moderately shallow central anterior chamber, and a flat peripheral anterior chamber. The ciliochoroidal detachment was postulated to displace the iris-lens diaphragm, resulting in the closed angle. Closure of the orbital fistula in the 17-year-old patient reduced the ciliochoroidal detachment and relieved the glaucoma, but visual acuity was reduced to 20/200. The glaucoma in the 73-year-old patient was relieved with topical instillation of timolol 0.5%, homatropine 5%, and systemic administration of acetazolamide. The fistula closed spontaneously, with relief of other ocular signs of the arteriovenous fistula.

Several forms of glaucoma may be found in eyes with an arteriovenous fistula. An open angle with increased episcleral pressure is the most common form.[1-5] In eyes with marked ischemia, rubeosis of the angle has led to neovascular glaucoma.[6,7] One case of acute closed-angle glaucoma caused by pupillary block after a carotid-cavernous fistula has also been reported.[8] I studied two distinctive cases of acute closed-angle glaucoma complicating arteriovenous fistulas in which the mechanism of the glaucoma appeared to be anterior displacement of the lens-iris diaphragm caused by an annular ciliochoroidal detachment.

Accepted for publication Oct. 14, 1988.

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Case Reports

Case 1

A 17-year-old girl had right-sided proptosis and increased intraocular pressure. She had a history of chronic glomerulonephritis, which required dialysis. Seven months before examination, she developed mild proptosis of the right eye. This was diagnosed as a retrobulbar arteriovenous fistula and was successfully closed by embolization. All signs and symptoms resolved. One day after streptokinase treatment for a clotted forearm graft used for dialysis, she developed marked proptosis and decreased vision in her right eye, prompting her referral.

On examination, visual acuity was R.E.: 20/80 and L.E.: 20/20. In the right eye (Figure), there was chemosis, a moderately shallow central anterior chamber with a flat peripheral chamber, and a clear lens. The left eye had a deep central anterior chamber. Intraocular pressure was R.E.: 40 mm Hg and L.E.: 11 mm Hg. In the right eye, gonioscopy showed complete angle closure and ophthalmoscopy, limited to the posterior pole, demonstrated dilated tortuous veins. The left eye was normal.

The patient was treated with timolol maleate 0.5%, one drop two times a day, and 250 mg of acetazolamide orally two times a day. Three days later, visual acuity had decreased to hand motions in the right eye. Ophthalmoscopy and ultrasonography showed a prominent serous retinal detachment and a large, annular ciliochoroidal detachment. Repeat radiologic embolization was not possible, and so she underwent neurosurgical closure of the arteriovenous fistula. One week after surgery, off all ocular therapy, visual acuity had improved to 20/200, the anterior chamber was of normal depth (equal to the fellow eye), intraocular pressure was 8 mm Hg, and the ciliochoroidal effusion had resolved. Gonioscopy demonstrated an open angle to the ciliary body in both eyes. Six months later, results of examination were unchanged.

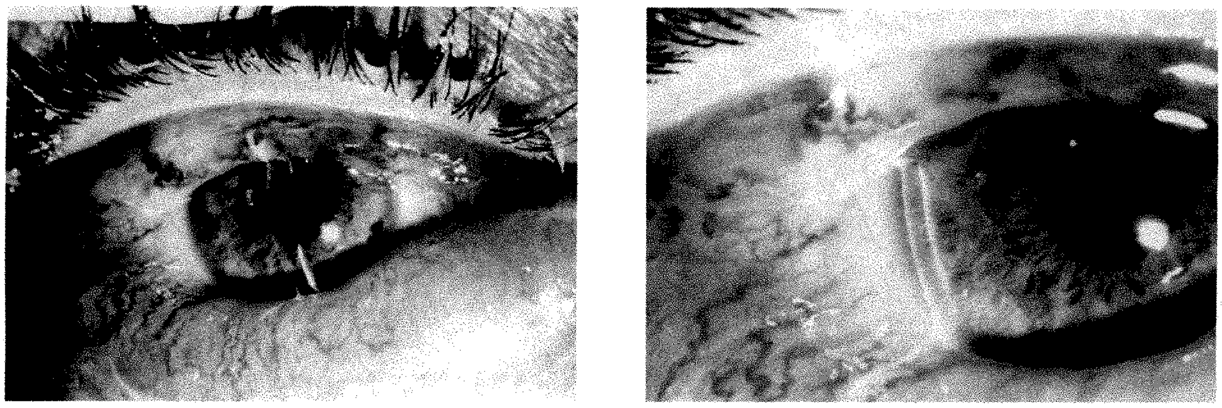

Figure (Fourman). Case 1, right eye. Left, Central anterior chamber depth appears moderately shallow. Right, Note flat peripheral anterior chamber.

Case 2

A 73-year-old woman was referred because of unilateral conjunctival engorgement, diplopia, a shallow anterior chamber, and increased intraocular pressure. Three weeks before referral, she developed bilateral sixth nerve palsy and right-sided third nerve palsy accompanied by bilateral conjunctival congestion and increased intraocular pressure. An arteriogram demonstrated a dural arteriovenous fistula originating from branches of the right internal maxillary artery. Her neurologic deficits and visual loss progressed, and she underwent embolization of the fistula. After surgery, intraocular pressure and visual acuity appeared to improve in the left eye but worsened in the right. A diagnosis of closed-angle glaucoma was made, and each eye was treated with pilocarpine 2% and argon laser peripheral iridotomy. The chamber angle of each eye opened to the ciliary body and the intraocular pressure decreased to R.E.: 14 mm Hg and L.E.: 17 mm Hg.

The patient was stable until one week later when she developed severe pain in the right eye, prompting her referral. On examination, visual acuity was R.E.: counting fingers and L.E.: 20/25. There was marked conjunctival congestion with tortuous vessels, eyelid edema, a shallow central anterior chamber, a flat peripheral chamber, and a clear lens in the right eye. The left eye was normal. A patent iridotomy, as determined by direct visualization and retroillumination, was present in both eyes. Intraocular pressure was R.E.: 32 mm Hg and L.E.: 17 mm Hg. B-scan ultrasonography showed an annular ciliochoroidal detachment in the right eye.

A diagnosis of choroidal effusion complicating an intracranial arteriovenous fistula was made. Treatment with homatropine 5%, one drop three times a day, timolol maleate 0.5%, one drop two times a day, and 250 mg of acetazolamide orally four times a day partially deepened the central anterior chamber, opened the angle, and lowered the intraocular pressure to 14 mm Hg. Three weeks later, the arteriovenous fistula spontaneously resolved with rapid resolution of all signs of orbital congestion involving the right eye. The ciliochoroidal detachment resolved, the chamber deepened to normal, and the intraocular pressure was 10 mm Hg. All therapy was stopped without relapse. One year later, her ocular status remained unchanged.

Discussion

Secondary glaucoma may occur in 6% to 100% of eyes with an arteriovenous fistula.[3-5] Previously described mechanisms for the increased intraocular pressure have included increased episcleral pressure,[4,5] angle closure caused by anterior segment neovascularization,[6,7] and angle-closure glaucoma caused by pupillary block.[8]

Increased episcleral pressure, resulting from a generalized increase in orbital venous pressure, is the most common cause of increased intraocular pressure in this disorder.[4,5] The increase in intraocular pressure may be equal to or greater than the increase in episcleral pressure. Examination of these eyes shows a normal anterior chamber, an open chamber angle,

and intraocular pressure ranging from 20 mm Hg to 57 mm Hg. Blood may be seen in Schlemm's canal.

In patients with large fistulas or after surgical correction, chronic angle closure caused by neovascularization of the anterior chamber has been described.[6,7] In these eyes, ocular perfusion is believed to be significantly reduced as compared to normal, resulting in ischemia and rubeosis. Cataract may develop. Visual prognosis is usually poor.

Harris and Rice[8] reported one case of acute closed-angle glaucoma with pupillary block after a carotid-cavernous fistula. The eye had a mid-dilated and fixed pupil. Results of B-scan ultrasonography were normal. Pilocarpine lowered the intraocular pressure and opened the angle to the scleral spur. After spontaneous closure of the fistula, the angle remained open and could not be occluded by pupillary dilation. The authors postulated that the increased venous episcleral pressure caused uveal edema, which allowed the eyes to be more susceptible to pupillary block and angle closure.

The patients described here had increased intraocular pressure, angle closure, a shallow central anterior chamber, a flat peripheral anterior chamber, and a ciliochoroidal detachment ipsilateral to a radiologically documented arteriovenous malformation. There were no signs of iris bombé or pupillary block in either eye, and a patent iridotomy was present in Case 2. Cycloplegia and aqueous humor suppressants successfully opened the angle in Case 2. After spontaneous or surgical closure of the fistula, there was prompt resolution of all abnormal findings in each patient.

This rare mechanism of angle closure without pupillary block caused by anterior displacement of the lens-iris diaphragm by a ciliochoroidal detachment, has been reported in association with scleritis,[9] pars planitis,[10] Harada's disease,[11] acquired immunodeficiency syndrome,[12,13] uveal effusion syndrome,[14-17] nanophthalmos,[18-20] panretinal photocoagulation,[21-23] and scleral buckling operations.[24,25] However, it has not been previously reported after arteriovenous fistula. Cogan[26] had noted bilateral serous retinal detachments occurring in a patient with an assumed but not proved carotid-cavernous fistula, but no mention of intraocular pressure, anterior chamber appearance, or gonioscopy was made. Woillez, Blervaque, and Dufour[27] reported decreased intraocular pressure in an eye with a carotid-cavernous fistula and choroidal detachment. Harbison, Guerry, and Wiesinger[28] noted increased intraocular pressure and a shallow anterior chamber in one patient with bilateral arteriovenous fistula and choroidal detachment, but the status of the chamber angle was not noted.

Differentiation between the possible mechanisms of glaucoma associated with an arteriovenous malformation is important to determine the therapeutic approach. In eyes with an open angle and increased episcleral pressure, aqueous suppressants are more effective than miotic agents.[5] Panretinal photocoagulation along with atropine, topical corticosteroids, and aqueous suppressants should be used in cases of anterior chamber neovascularization.[6,7] Pilocarpine or peripheral iridotomy would be expected to relieve angle closure caused by pupillary block.[8] In eyes with angle closure caused by a ciliochoroidal detachment, cycloplegia and aqueous suppressants are effective and pilocarpine is contraindicated. In all cases, closure of the fistula, either surgically or spontaneously, is associated with complete resolution of the glaucoma except in eyes with neovascularization.

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Ophthalmic miniature

"Come, we will see her. She has been waiting."

"At this hour of the night?" Taleniekov was surprised.

"There is no day or night for my grandmother. She said to bring you to her as soon as we arrived. We have arrived."

There *was* no day or night for the old woman sitting in the chair by the wood-burning stove, not in the accepted sense of sunlight and darkness. She was blind, her eyes two vacant orbs of pastel blue, staring at sounds and at the images of remembered memories.

Robert Ludlum, *The Matarese Circle*
New York, Bantam Books, Inc., 1979, p. 201

Immunohistologic Findings and Results of Treatment With Cyclosporine in Ligneous Conjunctivitis

Edward J. Holland, M.D., Chi-Chao Chan, M.D., Toichiro Kuwabara, M.D., Alan G. Palestine, M.D., J. James Rowsey, M.D., and Robert B. Nussenblatt, M.D.

Using immunohistochemical techniques, we studied ligneous conjunctival lesions from two patients. A significant immune reaction was detected that was characterized by activated T lymphocytes and focal accumulation of plasma cells and B lymphocytes. Immunofluorescent studies demonstrated that IgG was a prominent component of the amorphous hyaline material seen in these lesions.

After previous treatment methods had failed, both patients were treated with excisional biopsy and topical cyclosporine. Patient 1 had a dramatic response, with complete resolution of the lesions. Patient 2 had a significant improvement resulting in small, slow-growing recurrences instead of the rapid and extensive recurrences that occurred before treatment with cyclosporine.

LIGNEOUS CONJUNCTIVITIS is a rare disorder characterized by a chronic course of recurrent membranous lesions. The onset is usually in childhood, the disease is more often bilateral, and it may be associated with lesions of other mucous membranes in the mouth, nasopharynx, trachea, and vagina. The disorder has often been described to be more common in females, but a recent review of reported cases indicates a more equal male to female ratio.[1]

Previous histologic studies[2-6] have shown that the three major histologic components of these lesions are (1) an acellular, eosinophilic, periodic acid-Schiff-positive, hyaline material, (2) areas of granulation tissue, and (3) areas of cellular infiltration. These inflammatory infiltrates have been described in localized areas of ligneous lesions, often in association with new blood vessels. The components of the infiltrates include numerous plasma cells and eosinophils, with lesser numbers of lymphocytes, neutrophils, and mast cells.[7,8] Most reports describe the presence of neovascularization in areas consistent with granulation tissue. It is postulated that these new vessels are the origin of this hyaline substance.[4-6]

Treatment of this disorder has generally been unsuccessful. Topical hyaluronidase in conjunction with alpha-chymotripsin has been reported to be effective[2]; however, in other studies it has been of no benefit.[3-5] Other forms of topical therapy including antibiotics, corticosteroids, sodium cromoglycate, fibrinolysin, and silver nitrate have had limited effect. Cryosurgery, electrocoagulation, and surgical resection of the lesions usually result in rapid recurrence of the lesions within days to weeks.

We treated two patients with ligneous conjunctivitis with cyclosporine and studied the immunohistologic features of their lesions.

Case Reports

Case 1

A 20-year-old woman had a history of recurrent left dacryocystitis at age 1 year that was successfully treated with a probing of the left nasal lacrimal duct. The patient was without ocular problems until age 11 years when she had conjunctivitis of the left eye and an upper respiratory tract infection. Gram stain demonstrated a few gram-positive cocci. The patient was treated with topical sulfacetamide and when the conjunctivitis persisted she was

Accepted for publication Nov. 9, 1988.

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given bacitracin. Over the next few weeks a membrane formed over the palpebral conjunctiva of the lower eyelid. This was easily removed with forceps. However, the membrane recurred within a few days. The membrane was removed five more times during the next two months only to result in a rapid recurrence each time. The patient was subsequently treated with topical corticosteroids and antibiotics.

Over the next several years the membrane progressed to involve the upper palpebral conjunctiva of the left eye. She also developed scarring of the corneal stroma and vascularization. Visual acuity decreased to 20/80 in this eye. She was next treated with a variety of topical medications including corticosteroids, cromolyn 4%, hyaluronidase, and thiotepa without success. Cryosurgery was applied to the lower palpebral conjunctiva after resection of the membrane. One week after surgery the membrane recurred.

Over the next eight years, the lesions were resected several times only to recur within one to four weeks. During this time the patient used intermittent topical corticosteroids to relieve discomfort.

The patient was referred to the National Eye Institute at the age of 20 years. She had complaints of increased ocular discomfort and concern over the cosmetic deformity. On examination, visual acuity was R.E.: 20/16 and L.E.: 20/80. There was a membrane on the palpebral conjunctiva of the entire left upper eyelid, extending to the lateral canthus and over the lateral three fourths of the lower eyelid. Extending from the membrane were three nodular masses, one on the medial upper eyelid and two on the lower eyelid. There was also a white membranous lesion originating from the bulbar conjunctiva near the 3 o'clock meridian of the corneoscleral limbus. This lesion had a vascular stalk, was 7 mm in vertical length, and covered the lateral third of the cornea. This lesion could be elevated, disclosing vascularization and scarring of the corneal stroma. In the central and medial cornea there was subepithelial scarring (Fig. 1).

To improve the cosmetic deformity and decrease the ocular discomfort, the three nodular extensions of the palpebral conjunctival membrane and the bulbar conjunctival lesion were resected. The specimens were sent for histopathologic and immunohistochemical study. Postoperatively, the patient was treated with topical corticosteroids, hyaluronidase, cromolyn 4%, and gentamicin. White membranous lesions appeared over the resected areas within two days. These were easily removed with forceps, but continued to recur. Acetylcysteine 10% was added to the regimen. However, the lesions continued to enlarge. Based on findings of the immunohistochemical studies, topical cyclosporine, 20 mg/ml, was started and applied every six hours. The rate of enlargement was significantly altered, with only a moderate progression of the lesions occurring. Because of this response, the frequency of application was increased to every two hours during waking hours. This resulted in gradual resolution of the bulbar lesion over the next several weeks. The lateral canthal lesion became less vascularized and more atrophic. Two areas of growth on the palpebral conjunctiva of each eyelid progressed slowly. At six months after initiation of cyclosporine, each lesion was protruding a few millimeters beyond the eyelid

Fig. 1 (Holland and associates). Patient 1 before cyclosporine treatment. Left, Extensive ligneous lesions of the superior and inferior palpebral conjunctiva. Right, Ligneous lesion of the bulbar conjunctiva extending over the lateral third of the cornea.

margin. These two areas were again resected and the cyclosporine dose increased to every one hour while awake for a few weeks.

Over the next several months the patient was maintained on a regimen of cyclosporine and topical corticosteroids every four hours. The conjunctival lesions did not recur. Small atrophic scars were noted in the areas of the previous ligneous lesions.

The topical cyclosporine and corticosteroids were gradually tapered. At last examination, two years since the initiation of treatment and one year after discontinuation of all medications, there had been no recurrence of the ligneous lesions (Fig. 2). Serum cyclosporine levels obtained at various times during treatment showed no significant serum level of the drug.

Case 2

A 2-year-old girl had had bilateral conjunctivitis at 10 days of age. The patient was treated with topical antibiotics. Within a few days membranous lesions appeared on the palpebral conjunctiva of all four eyelids. Despite the topical therapy, the lesions progressed.

The lesions were resected and the histopathologic findings were consistent with ligneous conjunctivitis. The child required resection of the lesions every two months until treatment with cyclosporine; at the time of surgery she also received cryotreatment to the resected areas. CO_2 laser resection of the left upper eyelid lesions was attempted to provide a dissection plane across the tarsus and minimize the exudative response. However, the lesions continued to recur within several days of surgery.

A regimen of cyclosporine ointment, 40 mg/ml, four times a day to the right eye only was started. Over the next several weeks the lesions in this eye gradually became smaller and the membranes in the left eye continued to progress.

The child was then referred to the University of Minnesota. Examination under anesthesia disclosed diffuse thickening of all four eyelids. Localized nodular membranous lesions along with broader more extensive lesions were found overlying the palpebral conjunctiva of the right eye. The bulbar conjunctiva, except for the fornices, was without membranes. The palpebral conjunctiva of the left eye was more severely involved. A membranous vascularized lesion covered the entire conjunctiva of the upper eyelid, with areas of nodular protrusion. The lower eyelid had a similar appearance.

The ligneous lesions were resected as completely as possible and the specimens were sent for histopathologic and immunohistochemical study. On the evening after surgery, a regimen of topical cyclosporine, 20 mg/ml, every hour was started. The patient also received topical corticosteroids, hyaluronidase, gentamicin, and acetylcysteine 10% four times a day in both eyes. On the first postoperative day there was a mucus-like thin membrane overlying the palpebral conjunctiva on all eyelids. These were removed with cotton-tip applicators. Over the next few days the amount of mucus diminished and by the second week was absent.

The patient continued to receive topical cyclosporine drops every two to four hours for several weeks. Three months after surgery, small lesions recurred on the palpebral conjunctiva of the right upper and left lower eye-

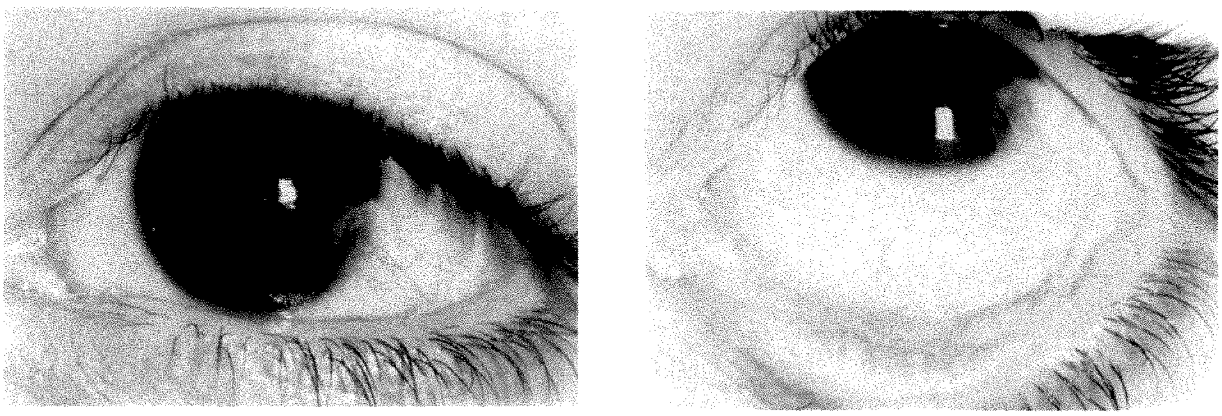

Fig. 2 (Holland and associates). Patient 1 after 15 months of treatment with topical cyclosporine. Left, Residual scar of cornea and bulbar conjunctiva. Right, Resolution of ligneous lesions of inferior palpebral conjunctiva. A small temporal symblepharon remains.

lids. These lesions were small and more localized than her previous recurrences. These lesions were excised and cyclosporine drops were continued. Examination after administration of anesthesia four months after surgery show no recurrence. At seven months, small lesions were seen on the palpebral conjunctiva of the right upper and the left lower eyelids. These were again resected.

At the most recent visit, the patient had been receiving topical cyclosporine for one year. Since treatment was started she has had small localized recurrences that are significantly different from the previous recurrences. They grow much slower and are smaller and more localized. She continues to receive cyclosporine drops every two to four hours, dexamethasone drops twice a day, and acetylcysteine 10% drops four times a day in both eyes. Serum cyclosporine levels to date have been undetectable. Serum creatinine levels have not changed.

Material and Methods

All freshly excised specimens were immediately divided into several portions. One part of each specimen was snap frozen and embedded in OCT compound. Frozen serial sections 6 μm thick were prepared using the avidin-biotin-peroxidase technique.[9] The primary antibodies were monoclonal antibodies prepared against human pan T lymphocytes (Leu 4), T helper/inducer lymphocytes (Leu 3a), T helper/inducer lymphocytes with inducer function (Leu 8), T suppressor/cytotoxic cells (Leu 2a), T suppressor/cytotoxic cells with suppressive function (Leu 15), B lymphocytes (Leu 14), bone marrow-derived monocytes (macrophages and epithelial cells, OKM 1 and Leu M5), and interleukin-2 (IL-2) receptors (anti-TAC). Mouse ascitic fluid containing 1 to 2 μg/l of protein served as a control. The secondary antibody was biotin-conjugated horse anti-mouse IgG. The avidin-biotin-peroxidase solution was applied, and the substrate was diaminobenzidine-nickel sulfate-hydrogen peroxide.

The remaining portions of each specimen were processed for routine light microscopy. Parafilm sections were stained with hematoxylin and eosin, periodic acid-Schiff, Congo red, Alcian blue, Masson trichrome, and colloidal iron.

Results

Microscopic examination of each of the three specimens from Case 1, which were taken before cyclosporine therapy, and from Case 2 showed similar histopathologic features. The conjunctival epithelium was disrupted and replaced by fibrinous necrotic tissue with an inflammatory cellular infiltration. The remaining epithelium showed irregularity, keratinization, degenerative changes, and thinning. Beneath the epithelium there was a layer of inflammatory tissue composed of mainly lymphocytes, plasma cells, some macrophages, and small dilated vessels. Small focal clusters of degenerative epithelial cells were noted in the deep substantia propria. Under the inflammatory cells in the deep substantia propria were large areas of amorphous, eosinophilic, hyaline material which stained positively with periodic acid-Schiff and Congo red without birefringence (Fig. 3). It stained negative for Masson trichrome and Alcian blue. Interspersed within the hyaline material were multiple cystic spaces, which did not appear as vascular channels. A few of these spaces contained lipid, as demonstrated by oil red O staining.

Immunohistopathologic studies showed that the cellular infiltrate was composed mainly of T lymphocytes, with the ratio of T helper/inducer to T suppressor/cytotoxic cells being approximately 3:1. Among the T helper/inducer cells, T inducer cells were seen in high concentration adjacent to B lymphocytes. Most T lymphocytes (75%) had IL-2 receptors. B lymphocytes were located focally in areas of plasma cells (Fig. 4).

Immunofluorescent techniques demonstrated that the major components of the hyaline material in the substantia propria were immunoglobulins (Fig. 5). IgG was the most prominent, with staining for both light and heavy chains, but primarily for κ-light chains. Some fibrin and fibrinogen staining was also seen. Laminin and fibronectin were mainly seen surrounding the vessels. The amount of collagen types I, III, and IV were insignificant as compared to normal conjunctival controls.

Histopathologic findings of the two palpebral conjunctival masses from Case 1 obtained after six months of topical cyclosporine therapy demonstrated changes in the epithelium similar to those seen before therapy. The amorphic hyaline material was also present, but to a

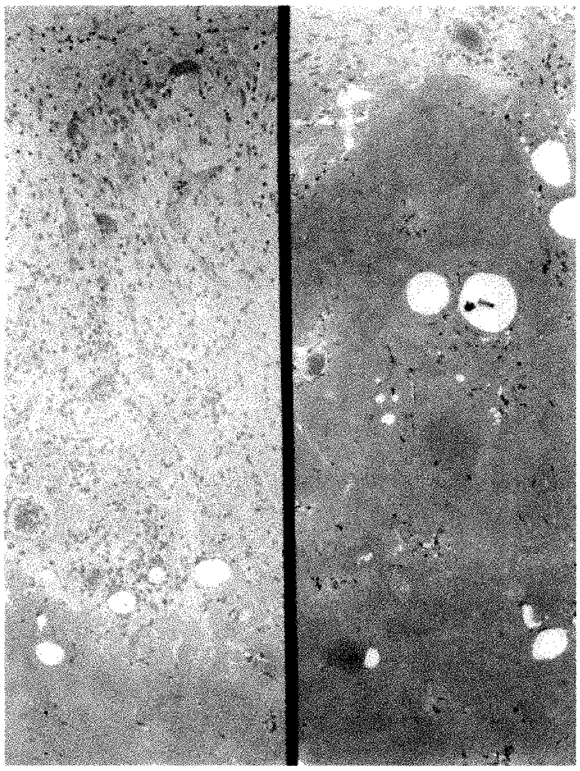

Fig. 3 (Holland and associates). Left, Layer of granulation tissue containing numerous inflammatory cells located between degenerative epithelium and amorphous material (hematoxylin and eosin, ×100). Right, Thick layer of amorphous, hyaline material underlying the inflammatory cells (Congo red, ×100).

lesser degree. In contrast to the first set of biopsy specimens, there was considerably less inflammatory cell infiltrate.

Immunohistochemical study of the specimens obtained after six months of topical cyclosporine therapy in Case 1 demonstrated significant changes in the cellular infiltrate. The total number of T lymphocytes was decreased, with a change in the ratio of T helper/inducer to T suppressor/cytotoxic cells now increased to approximately 6:1. Therefore, the most dramatic drop in the T cell population was seen in the T suppressor/cytotoxic cells. Additionally, most T lymphocytes (90%) lacked IL-2 receptors. A decrease in the number of B lymphocytes and plasma cells was also seen.

Discussion

We detected a significant immune reaction on immunohistochemical study of ligneous conjunctival lesions, which may have an important role in the chronicity of this entity. This inflammatory response was characterized by the presence of new blood vessels and activated T lymphocytes (anti-TAC). T helper/inducer cells (Leu 3a) were in greater concentration than T suppressor/cytotoxic cells. The accumulation of plasma cells, B and T lymphocytes, may have been part of an exaggerated immune response. Immunofluorescent studies demonstrated that

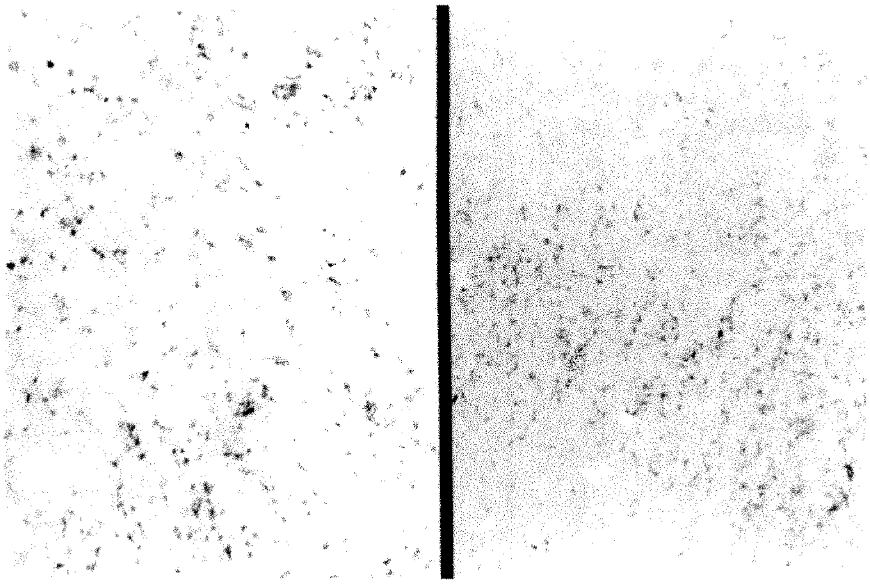

Fig. 4 (Holland and associates). Left, Immunohistochemical examination showed that most inflammatory cells bore T lymphocyte markers (Leu 4) (avidin-biotin-peroxidase, ×100). Right, Area of B lymphocyte (Leu 14) aggregation within granulation tissue layer (avidin-biotin-peroxidase, ×100).

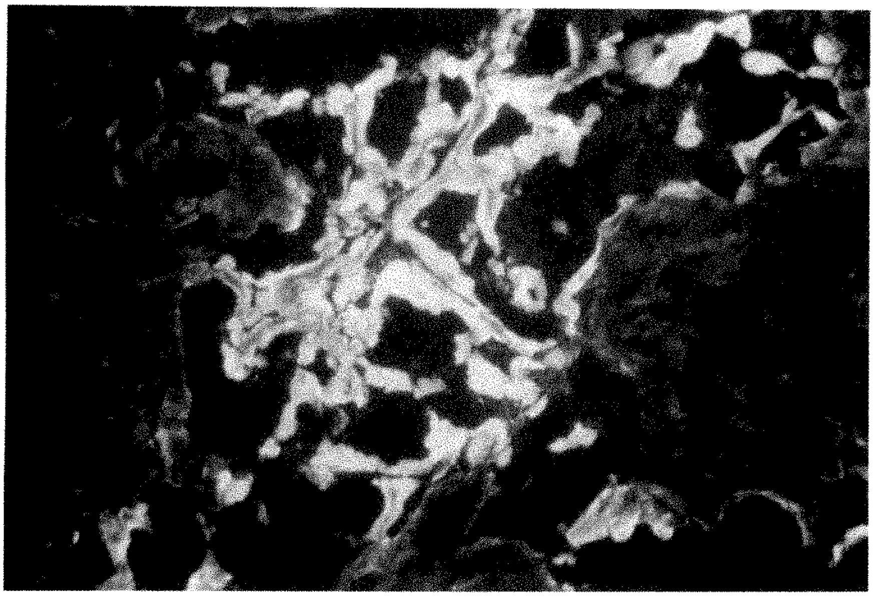

Fig. 5 (Holland and associates). Hyaline material staining positive for IgG (immunofluorescences, ×630).

in these patients IgG, but not collagen, was a prominent component of the amorphous hyaline material that is often seen in these lesions.

The pathogenesis of ligneous conjunctivitis is not known. Numerous causes have been proposed including autoimmune reaction, trauma, hypersensitivity reaction, genetic disorder, and secondary response to a viral or bacterial infection. Cooper, Kazdan, and Cutz[7] hypothesized that the abundant hyaline material typically found in the ligneous lesion may result from mast cell degranulation. The frequent presence of eosinophils along with mast cells gives support to the possibility of a hypersensitivity reaction. Previous reports[2,4] describe mucopolysaccharide as a major component of these lesions. This is postulated to be the result of a disturbance in conjunctival metabolism or may result from an exaggerated tissue response to trauma. Other studies[3,10] indicate that the hyaline material is largely made up of fibrin and the acid mucopolysaccharide present is located only in adjacent granulation tissue. Abnormal vascular permeability has also been suggested as the source of the various components of the ligneous lesion. Melikian[5] postulated that a serofibrinous transudate from conjunctival neovascularization undergoes subsequent coagulation, with the resulting formation of granulation tissue and accumulation of the hyaline material. This material becomes hard and the membrane is formed. Hidayat and Riddle,[6] in their review of the histopathologic features of 17 cases, hypothesized that the amorphous material was made up of albumin, fibrin, and immunoglobulin resulting from hyperpermeability. They found the lesions to contain abnormal blood vessels with wide gaps between lining endothelial cells.

From the findings in this study we postulate that an exaggerated inflammatory response, possibly following conjunctival epithelial injury, may be part of the cause of the disease in these patients. Epithelial degeneration occurring after minor trauma or infection may precipitate an inflammatory response. Indeed, degenerated epithelial cells were seen in the present study. T helper/inducer lymphocytes that occur as part of the inflammatory response may lead to recruitment of B lymphocytes and plasma cells. It is possible that the abundant, amorphous hyaline material seen in these lesions may be the result of liberated IgG from plasma cells or serum leaked from the neovascularization. Additionally, abnormal fibroblasts in the substantia propria may not produce collagen, but rather mucopolysaccharide, fibrin, or amyloid-like material. Accumulation of this hyaline material may further propagate the immune reaction.

Because of the immunohistologic findings and our patients' failure to respond to other therapies, topical cyclosporine was initiated. The immunosuppressive action of cyclosporine centers around the interference of T lymphocyte activation. Cyclosporine interferes with

the T lymphocytes' ability to produce the lymphokine IL-2 or respond to IL-2 by preventing the formation of specific IL-2 receptors.[11] This lymphokine is thought to be the primary path by which T lymphocytes continue to recruit and activate new T cells. The expression of IL-2 receptors is critical for the T cells' capacity to respond to this lymphokine.

Both patients appeared to have a beneficial response to cyclosporine. Before initiation of this treatment, Patient 1 had had a ten-year course and Patient 2 a two-year course of recurring lesions, without significant improvement with all other modes of therapy. Both had had several excisional biopsies which resulted in the recurrence of the lesions within days to weeks. In Patient 1, cyclosporine was administered every four hours initially and resulted in a much slower recurrence of the lesion compared to after previous excisions. After this favorable response cyclosporine was given every one to two hours, which resulted in complete resolution of the ligneous lesions. Patient 2 has had small recurrences requiring three excisional biopsies during her one-year treatment period. Again, these lesions are much smaller and slower growing than the rapid and extensive recurrences that occurred before initiation of cyclosporine.

Immunohistochemical analysis of a lesion resected after six months of topical cyclosporine therapy supports the immune role of this entity. A significant decrease in the total number of T lymphocytes was found, with the greatest decrease occurring in the T suppressor/cytotoxic cell subpopulation. Also of interest was the absence of IL-2 receptors on the T cells. Finally, a decrease in the number of B lymphocytes and plasma cells occurred. These results indicate the local effect cyclosporine has on the immune response. Cyclosporine does not eliminate the existing T cells, but rather, through its action on the production of IL-2 or its receptors, interferes with the activation and the recruitment of additional T cells. The marked reduction of T suppressor/cytotoxic cells that was seen was a secondary effect, as these cells are recruited by activated T cells. This has been shown to occur in the rat model of experimental autoimmune uveitis when treated with systemic cyclosporine.[12]

Ligneous conjunctivitis may have more than one cause, as there has been disagreement as to the histologic features described by various investigators. This may be the result of the mixture of inflammatory reactions and various products of abnormal epithelia and fibroblasts. The limitations of evaluating a treatment in only two patients are obvious; however, in a rare disorder such as ligneous conjunctivitis and in view of the favorable response that these patients had we consider the treatment results noteworthy. The results of the immunohistochemical studies before and after treatment with cyclosporine in Patient 1 support the hypothesis of local immune response in the pathogenesis of this disorder. We, therefore, will continue to evaluate cyclosporine therapy combined with excisional biopsy in other patients with this condition.

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Acute Hydrops in Pellucid Marginal Corneal Degeneration

John B. Carter, M.D., Dan B. Jones, M.D., and Kirk R. Wilhelmus, M.D.

Three patients had pellucid marginal corneal degeneration complicated by corneal edema. The corneal edema appeared to be a result of a break or detachment of Descemet's membrane as a result of increasing corneal ectasia. The disruption in Descemet's membrane began just above the inferior, crescent-shaped area of stromal thinning. Therapeutic modalities initially included hypertonic solution to determine whether corneal edema would resolve spontaneously, apparently by endothelial migration with healing over the break in Descemet's membrane. One patient required thermokeratoplasty and another penetrating keratoplasty for persistent stromal edema. Acute hydrops can occur with pellucid marginal corneal degeneration by a pathogenesis similar to other noninflammatory corneal thinning disorders such as keratoconus.

PELLUCID MARGINAL CORNEAL degeneration is an uncommon, noninflammatory thinning disorder of the inferior peripheral cornea.[1] The cornea protrudes above the area of thinning, causing high irregular astigmatism. This stress can cause breaks in Descemet's membrane, which can result in acute corneal edema, or hydrops. Twelve cases of pellucid marginal degeneration complicated by stromal edema have been reported.[2-12] We studied an additional three such cases.

Case Reports

Case 1

A 52-year-old man was referred for progressive against-the-rule astigmatism. With spectacle correction, the refractive error was R.E.: −2.25 +3.75 × 163 and L.E.: −8.50 +4.75 × 180; visual acuity was 20/50 in both eyes. Both eyes had stromal thinning in a 1.5-mm wide zone immediately inside the inferior corneoscleral limbus. He was fit with combined soft and hard contact lenses but discontinued their use because of persistent discomfort despite several modifications.

Over the subsequent six years he had a painless decrease in vision in his left eye. He then developed a sudden onset of burning, photophobia, and decreased vision. Best-corrected visual acuity at that time was R.E.: 20/60 and L.E.: hand motions, with a refractive error of R.E.: −6.75 +3.00 × 175 and L.E.: −11.25 +6.00 × 180. Examination showed microcystic epithelial edema and marked stromal edema involving the inferonasal cornea (Fig. 1). An oblique break in Descemet's membrane was observed in the inferior cornea, just superior to the region of thinning. The edema slowly resolved on treatment with hypertonic saline ointment over a period of six months, and corneal flattening occurred. Visual acuity improved to 20/100 with −3.00 +3.00 × 90 in the left eye.

Case 2

A 67-year-old man had had poor vision in the right eye since infancy because of anisometropic amblyopia. Two months before examination

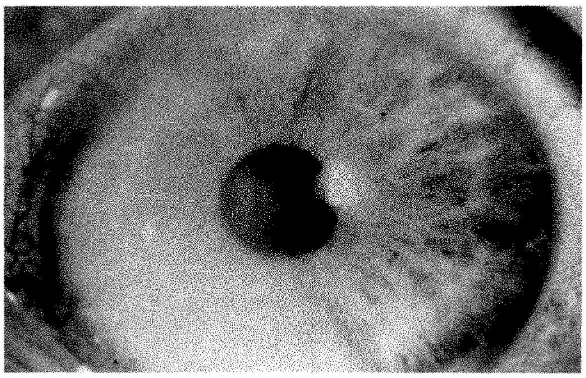

Fig. 1 (Carter and associates). Case 1. Acute stromal edema involves the area of corneal ectasia in a patient with pellucid marginal corneal degeneration.

Accepted for publication Nov. 7, 1988.

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he had noted increased tearing and light sensitivity of the right eye. Uncorrected visual acuity in the right eye was 6/200, not improved with refraction; best-corrected visual acuity in the left eye was 20/30 with −6.75 +6.00 × 25. Both eyes had axial corneal protrusion with inferior thinning. The right eye also had extensive microcystic epithelial edema and stromal edema centrally, and Descemet's membrane was detached in the edematous region.

Despite topical therapy with hypertonic saline, the patient required continuous patching for persistent photodysphoria and pain. After two months the area of edema was unchanged, and new vessels were seen in the anterior stroma in the region of the thinning inferiorly. Because of the poor visual prognosis from preexisting amblyopia, he underwent thermocauterization with multiple applications using wet-field cautery around the base and apex of the protruded cornea. On follow-up examination the ectasia was considerably reduced and Descemet's membrane had reattached. Vision was unchanged, but the corneal edema, pain, and light sensitivity had resolved.

Case 3

A 56-year-old woman had a 16-year history of slowly progressive inferior peripheral corneal thinning in both eyes. Over the previous year she had been using artificial tear preparations to try to reduce the discomfort of persistent corneal edema of the left eye.

On examination best-corrected visual acuity was R.E.: 20/50 and L.E.: 6/200. Spectacle correction was R.E.: −9.25 +5.75 × 93 and L.E.: −6.00 +9.25 × 84. The right eye had apical steepening, inferior peripheral thinning, and patchy, faint opacification of Descemet's membrane. The left eye had a similar area of crescent-shaped thinning inferiorly. Just above this zone was an area of prominent full-thickness stromal edema impinging on the visual axis (Fig. 2). Focal breaks and scrolls of Descemet's membrane with endothelial pleomorphism and cornea guttata were present in the edematous area.

An inferiorly decentered penetrating keratoplasty was performed in the left eye with a 9.5-mm graft into a 9.0-mm recipient site, surrounding the region of stromal edema and providing an adequate graft-host junction inferiorly. Histopathologic examination of the excised corneal button disclosed stromal edema and scarring. Descemet's membrane was wrinkled throughout and varied in thickness up to 25 μm. Focal areas of reduplication of Descemet's membrane forming scroll patterns were noted. The endothelium was attenuated in some areas and absent in others.

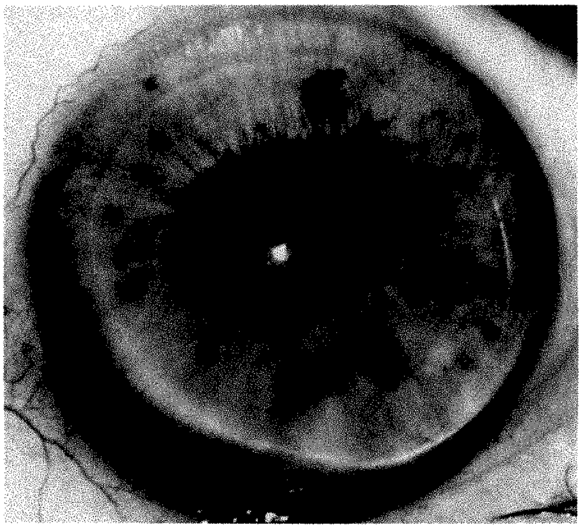

Fig. 2 (Carter and associates). Case 3. Crescentic corneal ectasia is present inferiorly in the left eye. The central stroma is scarred and edematous.

Allograft reaction occurred three months postoperatively and was treated with topical and oral corticosteroids. The corneal graft cleared progressively, and visual acuity improved to 20/40.

Discussion

Clinical descriptions of pellucid marginal corneal degeneration emphasize the crescent-shaped zone of stromal thinning in the inferior cornea, 1 to 2 mm central to the corneoscleral limbus.[1] The condition is typically diagnosed in the third and fourth decades, in similar numbers of men and women. Patients usually have decreased vision related to high irregular astigmatism.

Twelve cases of pellucid marginal degeneration with edema have been previously reported (Table).[2-12] Of these, eight had an identifiable break in Descemet's membrane. All three of our patients with pellucid marginal corneal degeneration complicated by corneal edema had a clinically visible break or detachment of Descemet's membrane.

Histopathologic findings in three cases of

TABLE
SUMMARY OF REPORTED CASES OF PELLUCID MARGINAL CORNEAL DEGENERATION WITH ACUTE HYDROPS

STUDY, PATIENT NO., AGE (YRS), SEX	DESCEMET'S MEMBRANE ABNORMALITY	THERAPY
Verrey[2]	Break with detachment	None
1, 23, F		
Etzine[3]	Break	None
2, 30, F		
Hallermann[4]	Unknown	None
3, 37, M		
Böles and Trux[5]	Unknown	Medical
4, 66, M		
Nagy and Vigvary[6]	Probable break	Medical
5, 57, M		
Krachmer[7]	Break	Penetrating keratoplasty
6, 48, F		
Rodrigues and associates[8]	Probable break	Penetrating keratoplasty
7, 54, M		
Parker and associates[9]	Break	Penetrating keratoplasty
8, 53, M		
Pouliquen and associates[10]	Break	Penetrating keratoplasty
9, 52, F		
Parunović and Ilić[11]	Unknown	Medical
10, 54, M		
Golubović and Parunović[12]		
11, 39, M	Break	Medical
12, 44, M	Unknown	Medical
Present study		
13, 58, M	Break	Medical
14, 67, M	Break with detachment	Thermocauterization
15, 56, F	Break	Penetrating keratoplasty

pellucid marginal degeneration complicated by edema have been previously reported. Rodrigues and associates[8] found an epithelium of irregular thickness, a Bowman's layer partially replaced by scar, stromal thinning and compression inferiorly, an intact Descemet's membrane, and partially absent endothelium. Parker and associates[9] noted epithelial thickening in the periphery, an irregularly scarred and mildly vascularized stroma, and a discontinuous Descemet's membrane. The breaks in Descemet's membrane were covered posteriorly by fibrous tissue and a new endothelial basement membrane, although the endothelium was absent from much of the specimen. The study by Pouliquen and associates[10] demonstrated breaks in Bowman's layer, disorganization of stromal collagen, and focal breaks in Descemet's membrane. The stromal edema was most marked in the region of the breaks in Descemet's membrane. Endothelial cells were noted to be migrating from the edge of the breaks to cover this disruption. In one of our patients (Case 3), histopathologic examination also showed apparent regeneration of Descemet's membrane over a preexisting break.

The mechanism of corneal edema in pellucid marginal degeneration appears to be a consequence of a break or detachment of Descemet's membrane with loss of the barrier function of the endothelium. These separations appear to be a result of the distortion of the ectatic cornea. This mechanism is consistent with the reports of breaks in Descemet's membrane and acute hydrops in keratoconus,[13,14] Terrien's marginal degeneration,[15] and keratoglobus.[16] Resolution of the edema apparently can occur by migration of endothelium across a break.

These cases demonstrate that acute hydrops can occur during the course of pellucid marginal corneal degeneration and is not a distinguishing feature among the noninflammatory corneal thinning disorders. Appropriate management initially includes conservative measures while endothelial migration and Descemet's membrane regeneration occurs. Of our three patients, one was treated conservatively and two required surgery. Of these two, the patient with amblyopia was treated with thermokeratoplasty, achieving a result that was both comfortable and cosmetically acceptable; the other underwent successful penetrating keratoplasty. While corneal surgery is a management option for persistent corneal edema, conservative measures and observation are first recommended for this complication of pellucid marginal corneal degeneration.

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The Management of Retinal Detachment Complicating Degenerative Retinoschisis

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We repaired six retinal detachments complicating degenerative retinoschisis by using simultaneous external subretinal fluid drainage and intraocular gas injection without a scleral buckle or vitrectomy. The outer wall breaks were 30 to 135 degrees in size, and in three cases, extended close to the arcade vessels. We achieved retinal reattachment and collapse of the schisis cavity at surgery in all six cases. In one case, the retina redetached postoperatively, but it was repaired with a scleral buckle and gas injection. This technique simplified the management of retinal detachments complicating degenerative retinoschisis, particularly those with large or posterior outer-layer breaks.

SYMPTOMATIC PROGRESSIVE retinal detachment complicating degenerative retinoschisis is rare,[1] but when present, may be associated with large or posterior outer layer retinal breaks.[2,3] The position and size of these breaks may make them difficult to manage with standard scleral buckling techniques.[2]

Meyers and associates[4,5] previously described a technique that allows simultaneous external subretinal fluid drainage and intravitreal gas injection. This has been useful in selected complex cases of retinal detachment. We used this technique without a scleral buckle or vitrectomy in six cases of retinal detachment complicating degenerative retinoschisis.

Material and Methods

We inserted a specially designed 27-gauge[5] or 30-gauge infusion needle through the pars plana and secured it with a 7-0 silk suture. We then selected and prepared a drainage site in the bed of the large outer-layer break so that both subretinal fluid and schisis cavity fluid could be drained. A preplaced suture was inserted. We then rotated the globe to allow the drainage site to be as dependent as possible while we drained the subretinal fluid. The surgeon monitored the drain site externally while the assistant gradually injected the gas in increments of 0.1 to 0.2 ml through the preplaced infusion needle, ensuring at all times that the eye was not too firm (Fig. 1). As soon as subretinal fluid drainage stopped, we immediately terminated the gas injection and closed the drainage site with the preplaced suture. We used various concentrations of sulfur hexafluoride (SF_6), depending on the amount of expansion desired.

In these cases we did not perform a simultaneous scleral buckle or vitrectomy. However, if an indentation from a scleral buckle is desired, we would either terminate the gas injection before the subretinal fluid drainage stopped

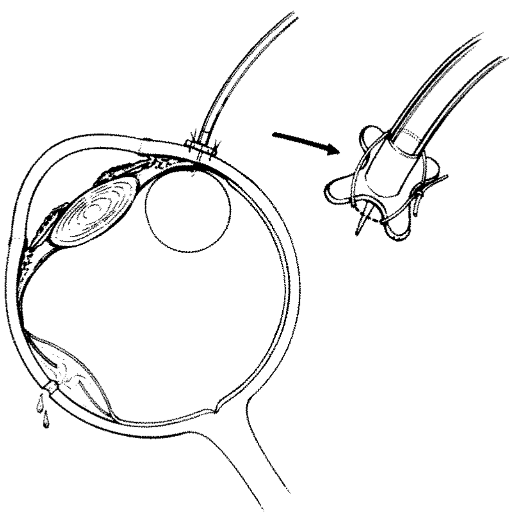

Fig. 1 (Ambler and associates). Gas is injected through a preplaced infusion needle as fluid is simultaneously drained through the dependent sclerotomy.

Accepted for publication Nov. 17, 1988.
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and complete the drainage before pulling up the buckle and band, or we would continue the gas injection until the retina was flat and then later remove enough gas to allow the buckle to be pulled up, as we have in cases of retinal detachment without retinoschisis.

Case Reports

Case 1

A 61-year-old woman had undergone a right scleral buckling procedure one week previously that had failed. Best-corrected visual acuity was R.E.: 20/200 and L.E.: 20/25. In the right eye, there was a 120-degree inferotemporal retinal detachment (Fig. 2). The macula was detached. There was an inferotemporal retinoschisis extending 105 degrees circumferentially and posteriorly to the arcade vessels. We observed a 105-degree outer-layer retinal break, with its posterior margin to the arcade vessels. There were multiple small inner-layer breaks. The left eye had retinoschisis in the superotemporal quadrant extending 50 degrees circumferentially and to slightly posterior to the equator. There were five medium-sized, round outer-layer breaks, but no retinal detachment.

In the right eye, we removed the sponge under the preexisting No. 279 silicone exoplant, performed cryopexy to the anterior and lateral sides of the giant outer break, performed simultaneous external subretinal fluid drainage and intraocular gas injection (10% SF_6), and slightly tightened the encircling band. We performed argon laser photocoagulation to the posterior margin of the large outer-layer retinal break on the first postoperative day.

Twenty-seven months postoperatively, the retina was attached and the schisis cavity remained collapsed. Visual acuity in the right eye was 20/40+1. There was a mild epiretinal macular membrane. The retinoschisis and outer-layer breaks in the left eye were unchanged.

Case 2

A 71-year-old man had a best-corrected visual acuity of 20/20 in his right eye and an asymptomatic peripheral atrophic hole with a small amount of subretinal fluid but no retinoschisis. In the left eye, best-corrected visual acuity was counting fingers at 2 feet and there was a bullous, 210-degree temporal retinal detachment, a 70-degree superotemporal retinoschisis, and several small inner-layer breaks overlying a large, round 30-degree outer-layer break, which extended to the arcade vessels (Fig. 3). We successfully repaired the detachment and flattened the schisis cavity by performing cryopexy and simultaneous external drainage of subretinal fluid and intraocular gas injection (25% SF_6) without a scleral buckle.

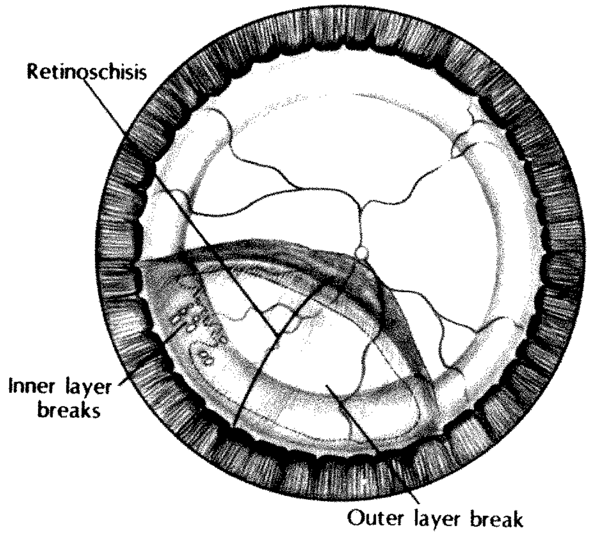

Fig. 2 (Ambler and associates). Case 1. Inferotemporal retinal detachment with retinoschisis, a large outer-layer break and multiple small inner-layer breaks.

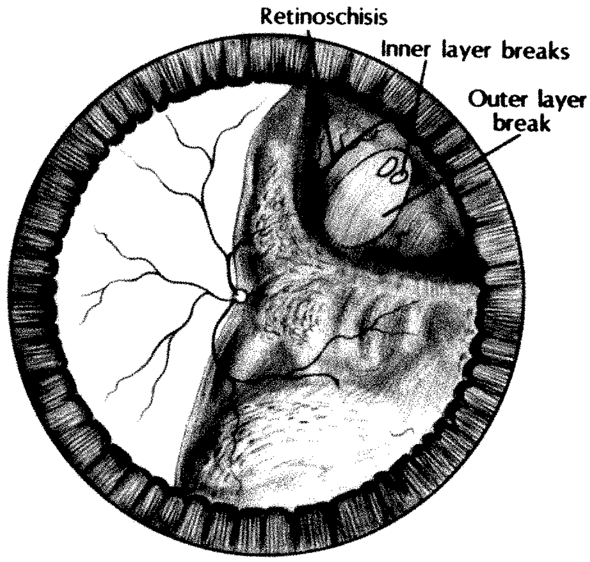

Fig. 3 (Ambler and associates). Case 2. Bullous temporal retinal detachment with superotemporal retinoschisis, a large outer-layer break, and several small inner-layer breaks.

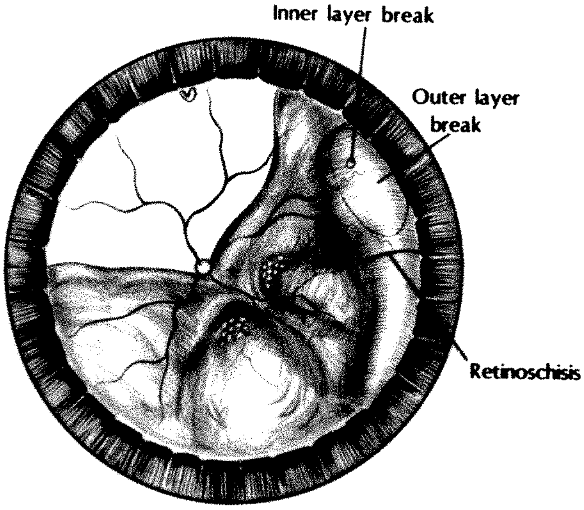

Fig. 4 (Ambler and associates). Case 3. Bullous three-quadrant retinal detachment with temporal retinoschisis and a large outer-layer break.

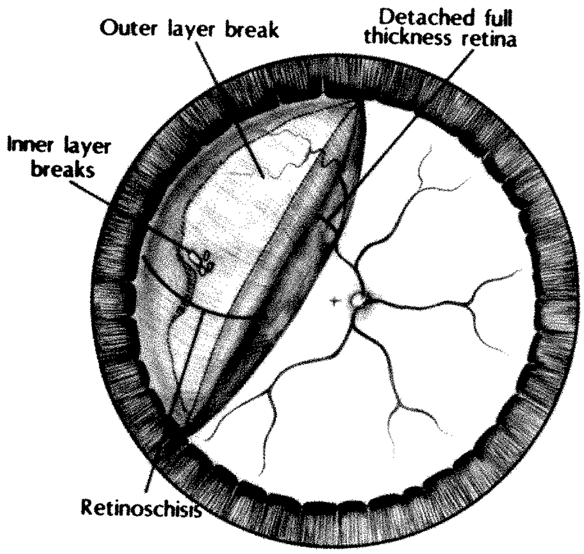

Fig. 5 (Ambler and associates). Case 4. Temporal retinal detachment with a large area of retinoschisis, a giant outer-layer break and several small inner-layer breaks.

Three and a half months postoperatively, visual acuity in the left eye was 20/40 and has remained unchanged two years postoperatively. The retina was attached and the schisis cavity was collapsed. There was a mild epiretinal macular membrane.

Case 3

A 67-year-old man had a one-week history of symptomatic left retinal detachment. Best-corrected visual acuity was L.E.: 20/400 and R.E.: 20/50. In the left eye, there was a 255-degree bullous retinal detachment, with the macula detached. There was a 120-degree temporal retinoschisis that extended behind the equator and a 45-degree superotemporal outer-layer break that extended 2 to 3 disk diameters behind the equator (Fig. 4). There was one small inner-layer break. There was also one small horseshoe tear in flat retina. The right eye had a 60-degree retinoschisis with a small peripheral outer-layer break but no retinal detachment. We performed retinal cryopexy and simultaneous drainage of subretinal fluid and intraocular gas injection (25% SF_6) without a scleral buckle. Intraoperatively, postoperatively, and at the most recent follow-up visit 15 months postoperatively, the retina was attached and the schisis cavity was collapsed. Best-corrected visual acuity was 20/40.

Case 4

A 69-year-old woman was asymptomatic. Visual acuity was 20/30 in both eyes. The left eye had a temporal area of retinoschisis without outer-layer breaks. The right eye, which had been pseudophakic with a posterior chamber intraocular lens for three years, had a bullous, 150-degree retinal detachment that spared the macula, retinoschisis temporally with a giant, 135-degree outer-layer break that extended to the arcade vessels, and several small inner-layer breaks (Fig. 5). The referring ophthalmologist had not noted any abnormality on retinal examination either before or after cataract surgery until the day before referral to us. In view of this and our finding of bullous retinal detachment posterior to the schisis cavity, we made a diagnosis of retinal detachment complicating degenerative retinoschisis. However, the lesion may have been a schisis detachment and may have been present and nonprogressive for a long time.

We performed simultaneous external subretinal fluid drainage and intraocular gas injection (33% SF_6) without a scleral buckle. This reattached the retina and collapsed the schisis cavity intraoperatively. We applied cryopexy after the gas injection to the flat retina.

Twelve months postoperatively the retina was flat with a collapsed schisis cavity, and visual acuity was 20/25.

Case 5

A 41-year-old woman had a three-day history of symptomatic right retinal detachment. Visu-

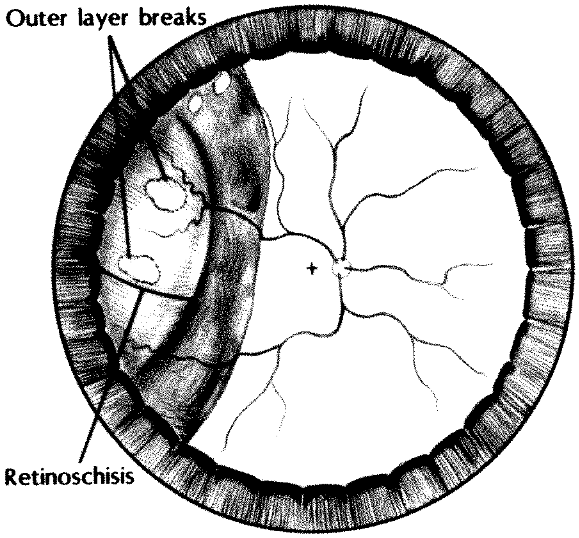

Fig. 6 (Ambler and associates). Case 5. Temporal retinal detachment with retinoschisis and two large outer-layer breaks. Two full-thickness retinal breaks are present superior to the area of retinoschisis.

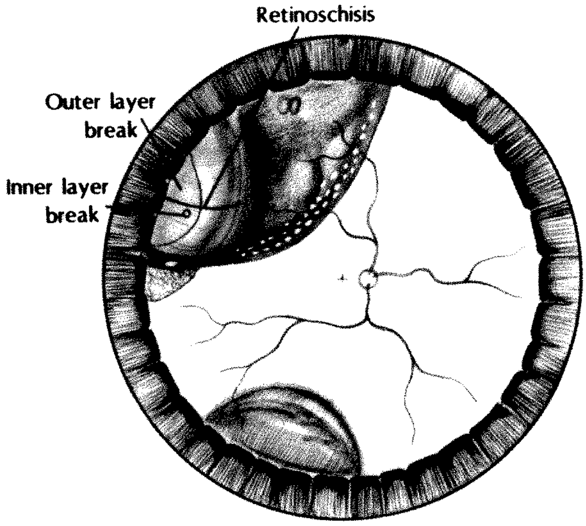

Fig. 7 (Ambler and associates). Case 6. Superotemporal retinal detachment with retinoschisis, a large outer-layer break, and one small inner-layer break. One small hole in full-thickness retina is present just inferior to the area of retinoschisis.

al acuity was 20/20 in both eyes. The left retina was normal. The right retina demonstrated a 120-degree temporal retinal detachment without macular involvement (Fig. 6). There was also a 75-degree temporal retinoschisis with two large outer-layer breaks. No inner-layer breaks were detected. Adjacent to the retinoschisis, there were two small, full-thickness retinal breaks. We performed retinal cryopexy and simultaneous drainage of subretinal fluid and intraocular gas injection (20% SF_6) without a scleral buckle. This reattached the retina and collapsed the schisis cavity. However, nine days postoperatively, a localized retinal detachment recurred in the superior region of the previous detachment. An inner-layer retinal break could be seen, and the detachment included a portion of one of the outer-layer retinal breaks.

Pneumatic retinopexy with injection of 100% SF_6 and laser photocoagulation flattened the retina, but on the first postoperative day, movement of the gas bubble away from the retinal breaks resulted in immediate redetachment of the retina. The next day, we successfully repaired the detachment with cryopexy, external drainage of subretinal fluid, scleral buckling with a localized No. 277 exoplant augmented with a radial half-thickness 7.5-mm sponge, and placement of an encircling band. The gas remaining from the pneumatic retinopexy was used for internal tamponade.

At the most recent follow-up visit, nine months postoperatively, the retina remained flat and the schisis cavity remained collapsed. Visual acuity was 20/30.

Case 6

A 72-year-old man had a three-week history of symptomatic retinal detachment in his right eye. Visual acuity was R.E.: 20/15 and L.E.: 20/20. In the right eye there was a 105-degree superotemporal retinal detachment with an attached macula (Fig. 7). There was a 45-degree temporal retinoschisis with a 30-degree outer-layer retinal break. There was one small inner-layer retinal break and a full-thickness retinal tear adjacent to the retinoschisis. There was also an inferior area of retinoschisis. The left eye demonstrated two temporal areas of retinoschisis, with the superotemporal area having three large outer-layer breaks but no retinal detachment.

We performed cryopexy and simultaneous external subretinal fluid drainage and intraocular gas injection (30% SF_6) without a scleral buckle. On postoperative day 1, there was a small amount of residual subretinal fluid in the inferior aspect of the previously detached area,

but the schisis cavity was collapsed. The subretinal fluid persisted over the succeeding five days, despite positioning of the gas bubble over the area of the retinal breaks. Laser photocoagulation was then applied posterior to the retinal breaks.

Over the next seven months, the residual subretinal fluid slowly decreased and, at the last examination, visual acuity in the right eye was 20/20. There was a small amount of residual subretinal fluid temporal to the macula, but the schisis cavity remained collapsed and all retinal breaks were closed.

Results

We achieved retinal reattachment and collapse of the schisis cavity at surgery in all six cases. In one case, the retina redetached nine days postoperatively but was successfully repaired with a scleral buckle after an unsuccessful pneumatic retinopexy. In all cases, the retina remained reattached and visual acuity was 20/40 or better at the most recent follow-up visit. We noted no iatrogenic retinal breaks, retinal incarceration, or other complications of this technique.

Discussion

Progressive symptomatic retinal detachment complicating degenerative retinoschisis should be differentiated from the much more common nonprogressive schisis-detachment.[1] True symptomatic progressive retinal detachments complicating retinoschisis may be associated with large or posterior outer-layer breaks. Their position and size may make them difficult to manage with standard scleral buckling techniques.[2] In two cases reported by Sulonen and associates[2] that were managed with scleral buckling, the buckles caused intolerable macular distortion or diplopia and had to be removed. These authors demonstrated considerable success in managing these difficult detachments by laser photocoagulation or cryopexy, fluid-air exchange (with vitrectomy as needed to create space for the air infusion), and postoperative face-down positioning. In similar cases, we successfully used the technique of simultaneous external subretinal fluid drainage and intraocular gas injection without vitrectomy, and obtained retinal reattachment and collapse of the schisis cavity at surgery in all six cases. In four of these cases, no scleral buckle or encircling element was applied. In one case (Case 1) in which an initial scleral buckling procedure had failed, this technique succeeded in reattaching the retina and collapsing the schisis cavity.

In the other case (Case 5) in which the technique was initially successful in reattaching the retina and collapsing the schisis cavity, redetachment occurred nine days later. We observed an inner-layer break that had not been detected preoperatively, elevation of a portion of an outer-layer break, and vitreous traction on the inner layer. The inner-layer break was considered to be a new break but it may well have been present before the surgery and not have been detected. We successfully reattached the retina with a scleral buckle with external drainage of subretinal fluid, but no gas injection was required since gas remained from the pneumatic retinopexy attempted the previous day.

We believe that simultaneous external drainage of subretinal fluid and intraocular gas injection has certain advantages over the sequential technique (injecting the gas after draining subretinal fluid) in managing some cases of retinal detachment, including retinal detachment complicating degenerative retinoschisis. It results in more complete drainage of subretinal fluid. It also avoids transient hypotony and thus, may decrease the risk of choroidal detachment and hemorrhage. In regard to retinal detachment complicating degenerative retinoschisis, we achieved near-total subretinal fluid drainage and complete collapse of the schisis cavity at surgery in all six cases. The schisis cavity remained collapsed in all five of the cases managed successfully with the technique.

The major risks of this simultaneous method, which have been previously discussed,[5] are retinal incarceration at the drainage site and iatrogenic retinal breaks. However, these risks are reduced by avoiding high intraocular pressure at the time of drainage, by keeping the eye rotated with the drainage site as dependent as possible, and, most important, by injecting the gas gradually and stopping the gas injection immediately when subretinal fluid drainage ceases.

Simultaneous external drainage of subretinal

fluid and intraocular gas injection simplifies the management of retinal detachment complicating degenerative retinoschisis with large or posterior outer-layer breaks. This technique also avoids, in many cases, the considerable adverse visual effects associated with posteriorly placed scleral buckles.

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OPHTHALMIC MINIATURE

But a biological organism reveals changes with time, which, though not always leading to deterioration, render it more and more difficult to obey all four conditions which stamp it as biological: namely reproduction, sensitivity to environmental changes, locomotion, and nutrition. It is the integration of various differential changes which mark the body as senescent.

A similar argument can be applied to the eye and vision. A premature arcus senilis, an early senile cataract, some deterioration in visual resolving power—none of these, taken singly, will betoken aging. But let them appear in combination: a delicate reference to "anno domini" will follow as surely as night follows day.

R. A. Weale, *The Aging Eye*
New York, Harper & Row, 1963, p. 5

Ultrastructural Studies of Vitreomacular Traction Syndrome

William E. Smiddy, M.D., W. Richard Green, M.D., Ronald G. Michels, M.D., and Zenaida de la Cruz, B.S.

We performed electron microscopic studies on seven specimens removed from the posterior retina at the time of vitrectomy for vitreomacular traction syndrome. Fibrous astrocytes were the predominant cell type in all cases. Fibrocytes were present in two cases and myofibrocytes were seen in three cases. Additional cellular and extracellular features included fragments of internal limiting membrane in six cases, old collagen in all cases, new collagen in one case, occasional macrophages in four cases, and fibrous astrocytes with myofibroblastic differentiation in one case.

THE VITREOMACULAR TRACTION syndrome is caused by vitreous traction on the macula, usually because of an incomplete posterior vitreous detachment. The most common morphologic configuration is a vitreous detachment peripheral to a zone where the cortical vitreous remains attached to the retina at the optic nerve head and the macula. Traction on the macula causes decreased vision, metamorphopsia, photopsia, and micropsia.[1-6] Clinical and operative evaluation has disclosed a visible epiretinal membrane, a layer of cortical vitreous, or both over the posterior pole.

Traction on the retina can be effectively eliminated by removal of the epiretinal membrane and condensed vitreous over the posterior pole.[7] We studied the electron microscopic features of epiretinal tissue removed from the posterior pole in seven cases of vitreomacular traction syndrome.

Accepted for publication Nov. 3, 1988.

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Material and Methods

The excised specimens were placed in buffered solution containing 4% formaldehyde and 2.5% glutaraldehyde and postfixed with 2% phosphate-buffered osmium tetroxide. After dehydration, the tissue was embedded in epoxy resin. Semithin sections were stained with paraphenylenediamine for phase-contrast microscopy. Ultrathin sections were doubly stained with uranyl acetate and lead citrate and examined in a transmission electron microscope.

Results

Clinical findings—The clinical features of our seven patients with vitreomacular traction syndrome (Table 1) were similar to those reported previously in a larger clinical series.[7] The average age was 61 years and there were five women and two men. Preoperative visual acuity ranged from 20/60 to 1/200, and averaged 20/200. Cystic changes in the macula were present in six cases (Fig. 1).

The vitreoretinal anatomy, observed during surgery, was of two basic patterns. In five cases, the cortical vitreous was detached in all four quadrants peripheral to the macula and optic nerve head. In two cases there was vitreous detachment in two to three quadrants with residual attachment to the macular area. The posterior vitreous surface was usually visible preoperatively where it was separated from the retina, but it was nearly transparent and could not be photographed. Postoperative visual acuity improved in five cases and was unchanged in two during a follow-up interval ranging from six to 21 months (mean, 7.7 months).

Pathologic findings—Transmission electron microscopy disclosed four morphologically distinguishable cell types as determined by previ-

TABLE 1
CLINICAL FEATURES OF PATIENTS WITH VITREOMACULAR TRACTION SYNDROME

PATIENT NO., AGE (YRS), SEX	DURATION OF SYMPTOMS (MOS)	PREOPERATIVE VISUAL ACUITY	VITREORETINAL ANATOMY*	POSTOPERATIVE VISUAL ACUITY	FOLLOW-UP (MOS)
1, 82, M	12	20/200	A	20/100†	13
2, 58, F	12	20/300	A	20/100†	10
3, 63, M	11	20/60	B	20/20	21
4, 69, F	3	20/80	A	20/70	6
5, 75, F	10	20/200	A	20/200	6
6, 47, F	1	1/200	A	20/400	9
7, 57, F	5	20/200	B	20/200	6

*A, peripheral posterior vitreous detachment in all four quadrants; B, detachment in two or three quadrants, but with zone of persistent attachment over the macula and optic nerve head.

†Postoperative visual acuity was limited by progressive nuclear sclerosis of the crystalline lens.

ously reported criteria (Table 2).[8-16] Fibrous astrocytes were the predominant cell type in all cases (Figs. 2 through 6) and were characterized by masses of intracytoplasmic intermediate-type 10-nm filaments, junctional complexes of the adherence type, and large, fusiform cells in groups or a monolayer showing polarization with basement membrane production. The fibrous astrocytes in one case contained aggregates of 5- to 7-nm intracytoplasmic filaments with fusiform densities (Fig. 5).

Other cell types were less frequent. Fibrocytes were identified in two cases and were characterized by abundant rough endoplasmic reticulum and a prominent Golgi complex, fusiform shape of the nucleus and cell body, and absence of intracytoplasmic filaments or basement membrane. Myofibrocytes were present in three cases and displayed features of fibrocytes but with aggregates of 5- to 7-nm subplasmalemmal cytoplasmic filaments with fusiform densities. Macrophages were present in four cases, identified by the presence of

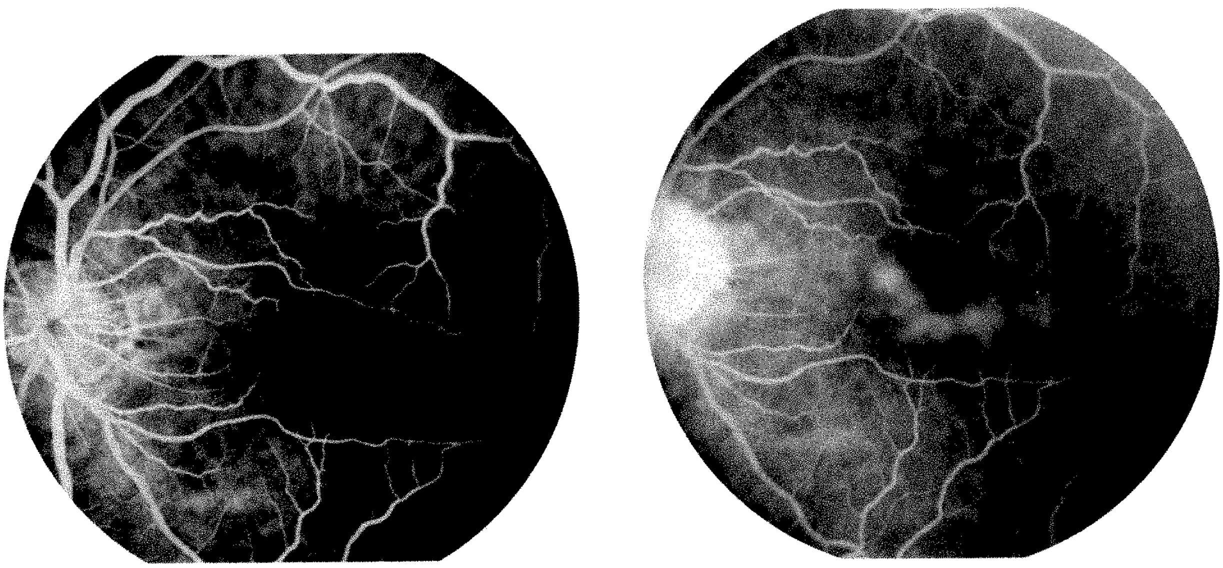

Fig. 1 (Smiddy and associates). Fluorescein angiographic appearance of Case 3. Early (left) and late (right) frames showing mild cystoid macular edema.

TABLE 2
ULTRASTRUCTURAL FEATURES OF VITREOMACULAR TRACTION SYNDROME

PATIENT NO.	CELL TYPES*		INTERNAL LIMITING MEMBRANE	COLLAGEN†	FIBROUS ASTROCYTES WITH MYOFIBROBLASTIC DIFFERENTIATION
	PREDOMINANT	OTHER			
1	FA	FC, MFB, M	Yes	New and old	No
2	FA	—	Yes	Old	No
3	FA	M	Yes	Old	Yes
4	FA	—	Yes	Old	No
5	FA	FC, MFB, M	Yes	Old	No
6	FA	MFB	Yes	Old	No
7	FA	M	No	Old	No

*FA, fibrous astrocytes; FC, fibrocytes; MFB, myofibroblasts; M, macrophages.
†Collagen was judged to be new if it measured greater than 16 nm in diameter and old if it measured less than 16 nm.

pleomorphic intracytoplasmic contents, irregularly shaped cell body and nucleus, and membrane-bound groups of granules of varying electron density.

Internal limiting membrane was present in six cases and had a smooth inner surface and an irregular outer surface. The smooth internal surface served as a substrate for the cellular growth in five of the seven membranes. In two cases (Cases 1 and 2), a thin layer of cortical vitreous with 15-nm diameter collagen was present between the internal limiting membrane and the cell layer.

Extracellular collagen was frequently associated with the cells and usually measured less than 15 nm in diameter, indicating that it was probably native collagen of the cortical vitreous.[17]

Discussion

The ultrastructural features of epiretinal membranes in this series of cases of the vitreomacular traction syndrome are similar to those in some cases of idiopathic epiretinal membranes. However, the clinical features of the vitreomacular traction syndrome are distinctly different from those of idiopathic epiretinal membranes. The vitreomacular traction syndrome is characterized by an incomplete posterior vitreous detachment,[1-7] whereas eyes with idiopathic epiretinal membranes involving the macula have a high rate of complete posterior vitreous detachment as shown clinically[16,18,19] and histopathologically.[8,10,20] Idiopathic epiretinal membranes have been noted to occur up to three years after the posterior vitreous detachment.[21]

One case of the vitreomacular traction syndrome has previously been studied histopathologically by light microscopy,[22] but in this case only a strand of vitreous was attached to the macula. There was no epiretinal membrane and there was considerable postmortem autolysis. This configuration of vitreomacular traction was found in only two of 16 eyes in a series of surgical cases reported previously,[7] and it was not present in the current series.

The electron microscopic features of the specimens in the current series included all cell types previously observed in epiretinal membranes except retinal pigment epithelium cells. The most striking finding was the predominance of fibrous astrocytes. Each major cell type may have particular roles or associations in various vitreoretinal disorders, but there probably is considerable overlap.

Retinal pigment epithelium cells predominate in cases of proliferative vitreoretinopathy[23] and cases of macular pucker after retinal detachment.[13,15,16,24] Although many of these epiretinal membranes also contain fibrous astrocytes,[9,12,25,26] no definite retinal pigment epithelium cells were identified in this series. Some studies suggest that fibrocytes and myofibrocytes are derived from retinal pigment epithelium cells,[23,27,28] and the contractile property of myofibrocytes is thought to account for

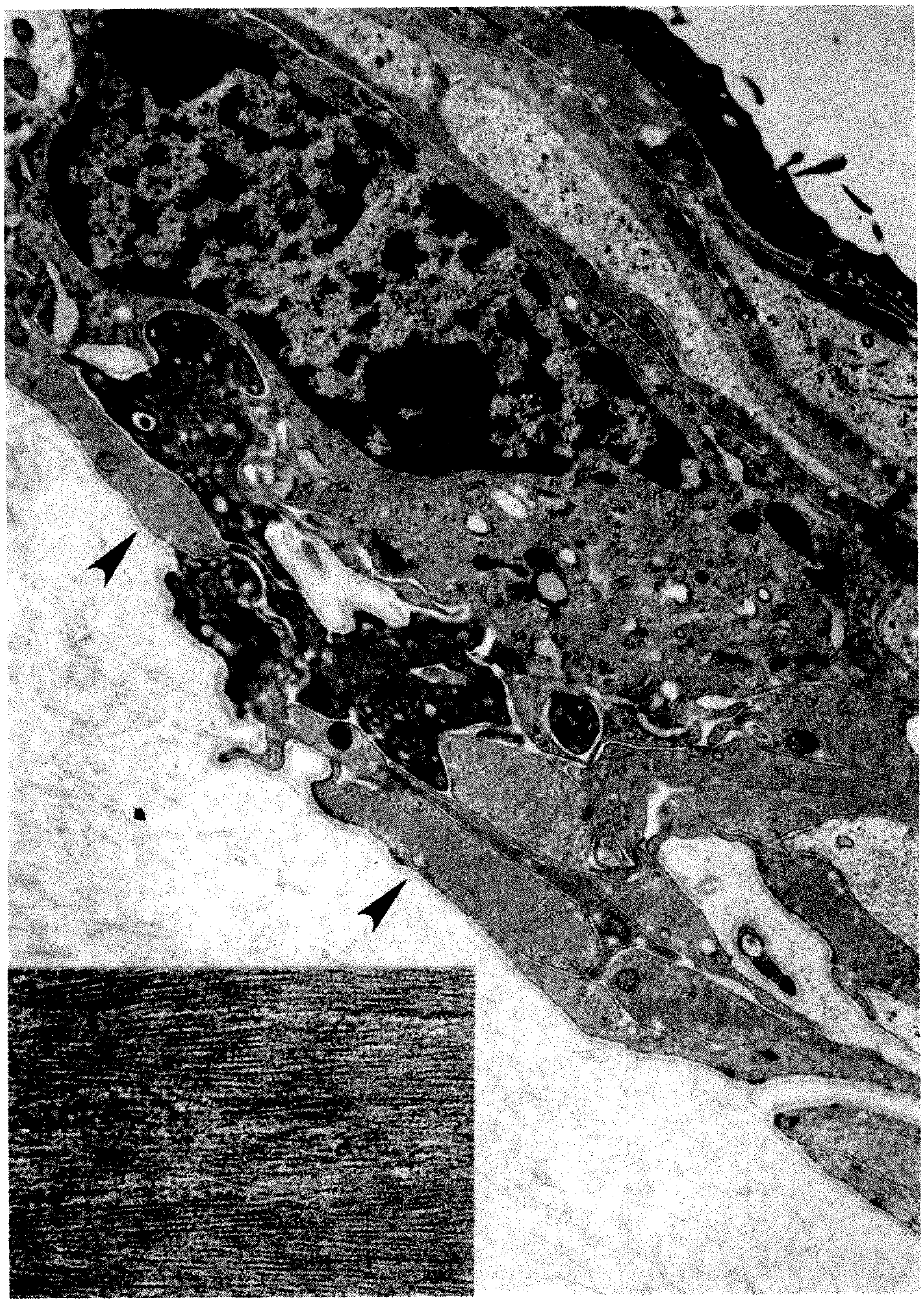

Fig. 2 (Smiddy and associates). Case 6. Membrane is composed of fibrous astrocytes that have a multilayered growth pattern with basement membrane (arrowheads) and characteristic 10-nm diameter intracytoplasmic filaments (inset) (× 14,000; inset, × 56,000).

clinical features of tractionon the retina. In this series, myofibrocytes were identified in two cases with especially severe clinical features of traction, but there was no evidence that they were derived from retinal pigment epithelium cells.

The predominance of fibrous astrocytes in the current series suggests that migration and

Fig. 3 (Smiddy and associates). Case 3. The epiretinal membrane is composed of a monolayer of fibrous astrocytes with basement membrane formation (arrowheads) on a collagen base. Marginal aggregates of 5- to 7-nm microfilaments (arrows) indicate myofibroblastic differentiation. A macrophage is also present (lower left) (×5,400).

proliferation of these cells may be a secondary response to vitreoretinal traction. In the absence of retinal breaks, fibrous astrocytes from the retina would have ready access to the inner retinal surface since the internal limiting membrane is discontinuous over the optic nerve head in normal eyes,[29] and small breaks in the internal limiting membrane may occur in other

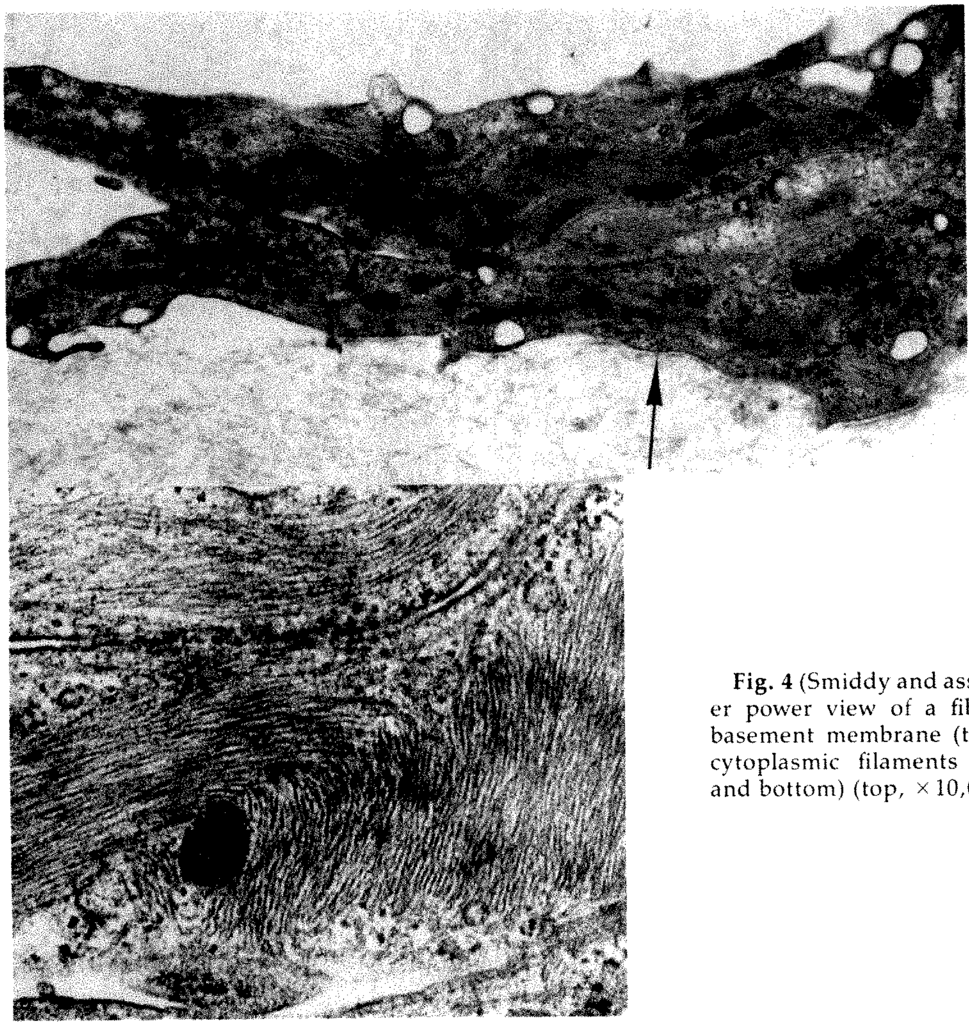

Fig. 4 (Smiddy and associates). Case 3. Higher power view of a fibrous astrocyte shows basement membrane (top, arrow) and 10-nm cytoplasmic filaments (between arrowheads and bottom) (top, × 10,000; bottom, × 44,000).

locations due to vitreous traction.[20] Focal epipapillary plaques of proliferating glial cells have been identified in 27% of eyes at autopsy[29] and in 46% of eyes with a posterior vitreous detachment.[30] Defects in the internal limiting membrane in the fovea, over retinal vessels, or elsewhere are clinically undetectable and they may be self-sealing so they would be undetectable by histopathologic study.[11] Traction by a partial posterior vitreous detachment serving as a stimulus for cell migration and proliferation has been hypothesized in other cases[10,20,29,31] The cases in the present series had chronic traction involving the macula and optic nerve head. The stimulus of vitreoretinal traction combined with the framework of the adjacent cortical vitreous may account for the migration and proliferation of glial tissue.

Another possible explanation for the cellular features in the tissue examined in this series is that epiretinal membranes may have formed before the posterior vitreous detachment occurred and caused a firm attachment between the cortical vitreous and the retina, thereby preventing separation in that region. However, the configuration of the zone of vitreoretinal traction in these cases is consistent[7] and unlike that encountered in other cases of epiretinal membranes. Posterior vitreous detachment is considered to predate the formation of idiopathic epiretinal membranes.[9]

In the current series, portions of internal limiting membrane were present in six of seven samples. Fragments of internal limiting membrane are also common in specimens of epiretinal membranes removed by vitreous surgery, but this is generally not associated with recurrent membrane proliferation.[13,16] This suggests

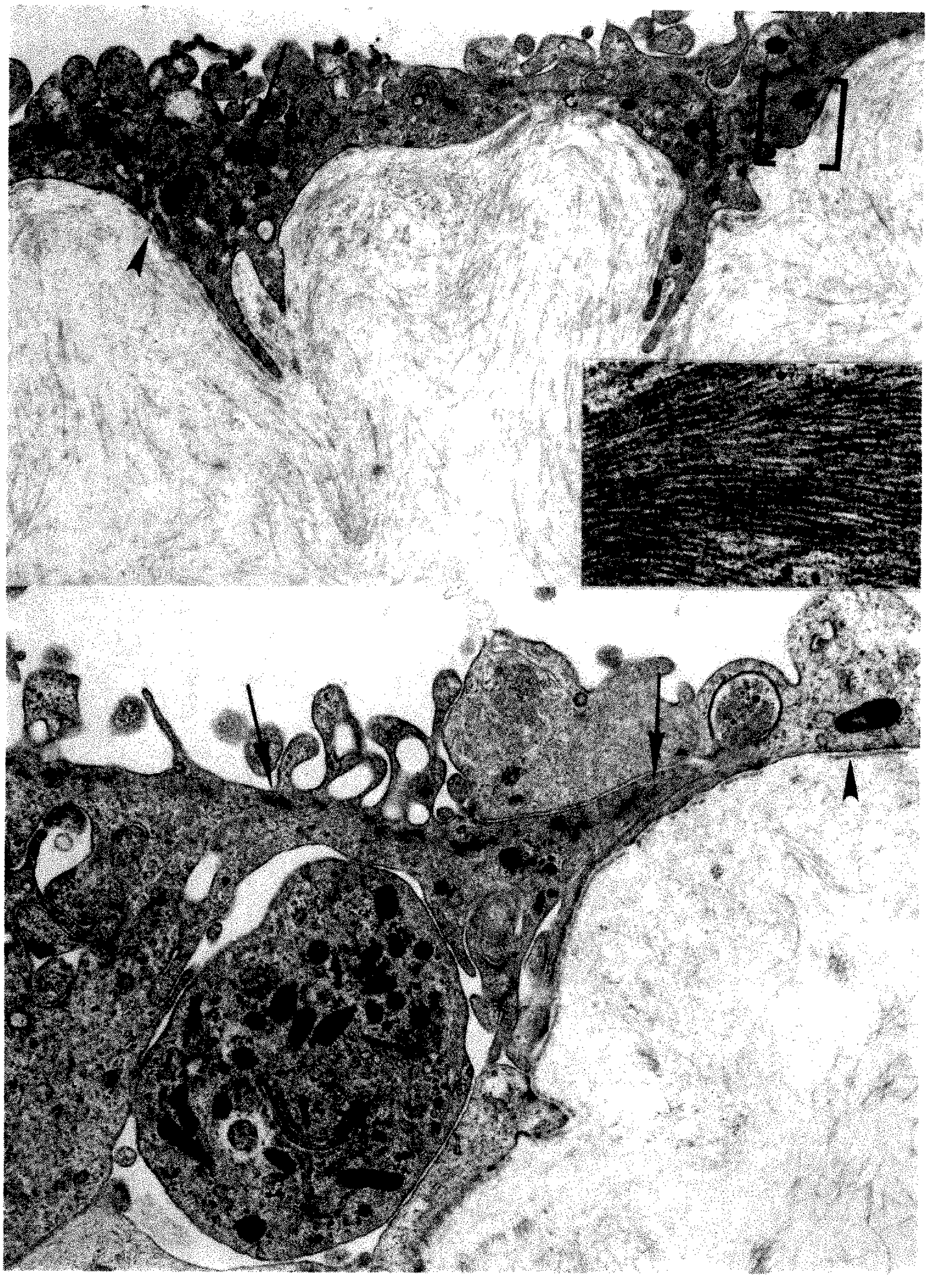

Fig. 5 (Smiddy and associates). Case 3. Top, Monolayer of fibrous astrocytes with basement membrane (arrowhead), aggregates of 5- to 7-nm microfilaments (arrow), and large bundles of 10-nm filaments (bracket and inset). Apparent contraction of cellular layer had a gathering effect on the collagen base (×10,000; inset, ×54,000). Bottom, Another fibrous astrocyte showing basement membrane (arrowhead) and an apparent tension line of marginal aggregates of 5- to 7-nm microfilaments with fusiform densities (arrows) (×12,000).

that breaks in the internal limiting membrane may not be the primary stimulus to outgrowth of glial tissue from the retina, and that structural factors such as vitreoretinal traction or biochemical stimuli may modulate the process of cell migration and proliferation.

The vitreomacular traction syndrome is a distinct clinical condition characterized by trac-

Fig. 6 (Smiddy and associates). Case 7. Top, Monolayer of fibrous astrocytes with basement membrane (arrows) and aggregates of 10-nm filaments (asterisk). A cell process of a fibrous astrocyte is lined by basement membrane (arrowheads) (×16,000). Bottom, Higher power view of fibrous astrocyte with basement membrane (arrow) and intermediate filaments (asterisk) (×40,000).

tion on the posterior retina resulting from an incomplete posterior vitreous detachment. As such, the clinical pathoanatomy is different from most cases of idiopathic epiretinal membranes and from eyes with an impending macular hole.[31] However, the ultrastructural features of epiretinal tissue from eyes with the vitreomacular traction syndrome are similar to those

from eyes with idiopathic epiretinal membranes, suggesting common features in pathogenesis.

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AMERICAN JOURNAL OF OPHTHALMOLOGY®

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EDITORIAL

Intraocular Pressure and Glaucoma

Alfred Sommer

Ever since von Graefe noticed that patients with a characteristic form of optic nerve damage had increased intraocular pressure, the two conditions have been inexorably linked in what is generally assumed to be a cause and effect relationship. We have even invented terminology and sought alternative explanations for seeming inconsistencies: "low tension" glaucoma for glaucomatous optic nerve damage in the absence of increased intraocular pressure and "ocular hypertension" for increased intraocular pressure in the absence of glaucomatous optic nerve damage. Whole volumes could be filled with arguments raised for and against the existence of these entities, their proper nomenclature, and perceived differences in origin and expression. Survey data that suggest a third or more "glaucoma" patients have "normal" intraocular pressure[1,2] are largely ignored.

A review of original clinical observations, from an epidemiologic perspective, suggests our present confusion may stem from preconceived notions that obscure basic unifying principles.

First, it is apparent that glaucomatous optic nerve damage is most common in eyes with high intraocular pressure. The validity of this conclusion is obvious among individuals in whom the pressure in one eye is considerably higher than in the other (from blunt trauma, uveitis, congenital abnormalities, and the like). If one of the two eyes has glaucomatous optic nerve damage, almost invariably it is the eye with the higher intraocular pressure. It is also apparent, but not nearly so obvious, that patients with primary open-angle glaucoma (by definition with glaucomatous optic nerve damage) rarely have pressures that are truly "low" (that is, several standard deviations below the population mean of 16 to 17 mm Hg). Hence, intraocular pressure is associated with glaucomatous optic nerve damage. In epidemiologic parlance, high intraocular pressure is a risk factor for glaucomatous optic nerve damage,

TABLE 1
RISK OF SUBSEQUENT GLAUCOMATOUS FIELD LOSS

BASELINE INTRAOCULAR PRESSURE (MM HG)	PERCENT DEVELOPING FIELD DEFECT*	RELATIVE RISK
< 16	0.8	1.0
16–19	1.4	1.7
20–23	3.1	4.0
≥ 24	8.4	10.5

*Over a one- to 13-year follow-up period. Modified from Armaly and associates.[3]

TABLE 2
RISK OF SUBSEQUENT GLAUCOMATOUS FIELD LOSS

BASELINE INTRAOCULAR PRESSURE (MM HG)	PERCENT DEVELOPING FIELD DEFECT*	RELATIVE RISK
21–25	2.7	1.0
26–30	12.0	4.4
> 30	41.2	15.3

*Mean follow-up of 43 months. Modified from David, Livingston, and Luntz[4] by Sommer.[5]

just as smoking is for lung cancer or high blood pressure is for stroke.

As with cancer and stroke, there seems to be a dose-response relationship between the risk factor (intraocular pressure) and the disease (glaucomatous optic nerve damage). Though available data are less than ideal, they are consistent: the higher the baseline intraocular pressure, the greater the risk of subsequently developing glaucomatous optic nerve damage. The Collaborative Glaucoma Study[3] permits estimation of subsequent risk of glaucomatous optic nerve damage for intraocular pressure below 16 to above 25 mm Hg. While the numbers are small and the interval of follow-up variable, the trend is obvious (Table 1). Subjects with intraocular pressure ranging between 16 and 19 mm Hg were at almost twice the risk of those whose pressure was lower; when pressure exceeded 23 mm Hg, the risk increased tenfold.

Reinterpretation of data from David, Livingston, and Luntz[4] indicates this dose-response relationship persists at higher levels[5] (Table 2). These and other studies[6-8] permit rough estimation of the relative risk of glaucomatous optic nerve damage among subjects whose original (baseline) pressure was above or below a single cutoff point. Again, the data are less than ideal, but their implications are consistent (Table 3).

These interpretations provide two important insights. Firstly, the direct relationship between intraocular pressure and risk of subsequent optic nerve damage strengthens the importance of intraocular pressure as a risk factor for glaucomatous optic nerve damage; as with cigarette smoking for cancer or systemic hypertension for stroke, it also suggests the relationship is causal. Secondly, it explains why a large proportion of all glaucomatous optic nerve damage occurs among individuals with "lower" intraocular pressure; it is simply because they comprise the bulk of the population. The risk of glaucomatous optic nerve damage at pressures below 22 mm Hg may be only one sixth that at higher pressures, but they apply to almost 20 times as many people (Table 3).

These extrapolations would suggest that most glaucomatous subjects have intraocular pressure lower than 22 mm Hg. There are many potential explanations for why, in reality, more might be related to "increased" intraocular pressure, including intermittent increases in intraocular pressure not detected at baseline measurement and (an unrecorded) sustained rise in intraocular pressure between baseline and subsequent development of glaucomatous optic nerve damage. There are also many reasons why patients with "lower" intraocular

TABLE 3
HYPOTHETICAL PROPORTION OF GLAUCOMA PATIENTS WITH PRESSURES ABOVE AND BELOW 21 MM HG

	INITIAL INTRAOCULAR PRESSURE		
	≤ 21 MM HG		> 21 MM HG
Relative risk of subsequent field defect (A)	1		6
Proportion of population (B)	.92		.08
Relative risk of glaucoma (A × B)	.92		.48
Ratio of glaucoma cases	2	to	1
Adjusted ratio of glaucoma cases*	1	to	1

*Assuming half of the glaucoma patients with an initial intraocular pressure of ≤ 21 mm Hg are subsequently found, on careful follow-up, to have (or develop) higher intraocular pressure.

pressures might appear to represent so small a component of clinical practice. Most importantly these include the biased referral and examination of patients detected by health fairs, optometrists, and even ophthalmologists because intraocular pressure was noted to be "increased." It is also probable that the rate at which axonal death occurs is directly related to intraocular pressure, and the higher the intraocular pressure, the more axons destroyed by any age. As a result, a greater proportion of subjects with "high" intraocular pressure will have clinically detectable glaucomatous optic nerve damage, the glaucomatous optic nerve damage will be more severe, and a larger proportion will ultimately become blind.

The foregoing indicates that there is no fixed intraocular pressure boundary below which one never develops glaucomatous optic nerve damage and above which one always does. The only intraocular pressure boundaries fixed are the extremes: the minimal pressure needed to prevent atrophy and the very high intraocular pressure resulting in venous and arterial occlusion. Between those extremes exists a broad range of pressure that is compatible (for varying durations in different individuals) with normal ocular physiology.

How then did we come to define 22 mm Hg, 25 mm Hg, 28 mm Hg, and the like, as "abnormal"? Recall that population surveys locate the "average" pressure at 16 to 17 mm Hg. If one wished to identify individuals at the greatest risk of glaucomatous optic nerve damage (present or future), it was most efficient to concentrate on the 5% or 1% of individuals with the highest pressures, which happen to coincide with pressures greater than 21 and 24 mm Hg, respectively. They were not chosen because they defined abnormal; they were chosen because they made the search for glaucomatous optic nerve damage more efficient.

If there is no such thing as an abnormal pressure, only pressures at which the risk of glaucomatous optic nerve damage is higher or lower than average, then there is no basis for the term low-tension glaucoma and no reason to search for a discrete mechanism to explain it. Nor does it make sense to wake patients at hourly intervals in search of a pressure exceeding 21 mm Hg (although establishing diurnal pressure curves may be useful for management), nor any value in choosing one specific intraocular pressure as a criterion for successful intervention or adequacy of control.

Intraocular pressure is not the only risk factor for glaucomatous optic nerve damage; the risk of primary open-angle glaucoma increases with age, is higher in some racial groups than in others, and may be associated with refractive status. While the close dose-response relationship between intraocular pressure and glaucomatous optic nerve damage supports other data suggesting a causal relationship, it does not explain why some people with high pressure never develop glaucomatous optic nerve damage any more than it explains why some people with low pressures do. Obviously other factors, genetic, medical, or environmental, play a modulating role. These urgently require further elucidation.

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LETTERS TO THE JOURNAL

Accurate Ultrasonic Biometry in Pseudophakia

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Accurate ultrasonic axial length measurements in eyes with an intraocular lens implant can be important when trying to identify the source of error in postoperative refraction.[1] It is also extremely important for determining axial length symmetry for cataract surgery in the second eye when preoperative measurements for the first eye are unavailable.[2]

Most of the ultrasonic biometers currently in use were designed for measurements in cataractous eyes and have assumed an average tissue velocity of approximately 1,550 m/sec.[3] In many of these units, the assumed velocity for aphakia cannot be changed, and none of them are accurate when an intraocular lens is present. We describe a simple method for accurately calculating the axial length in these situations.

The elapsed time for a sound wave to travel the axial length of the eye equals the time to travel through the intraocular lens plus the time to travel through the remaining ocular tissue. This can be expressed by the relationship shown in equation 1.

$$ET = \frac{T}{2{,}718} + \frac{AL - T}{1{,}532}, \qquad (1)$$

where ET = elapsed time, T = center plastic thickness of intraocular lens, 2,718 = ultrasound velocity in meters per second of polymethylmethacrylate at 37 C, AL = actual axial length, and 1,532 = ultrasound velocity in meters per second of the aphakic eye.[4,5] Using the typical assumed tissue velocity of 1,550 m/sec found on most instruments, the apparent axial length would be the product of this assumed velocity and the elapsed time, as shown in equation 2.

$$ALM50 = 1{,}550 \left(\frac{T}{2{,}718} + \frac{AL - T}{1{,}532}\right), \qquad (2)$$

where ALM50 is the apparent axial length at 1,550 m/sec.

Resolving equation 2 for the actual axial length (AL) yields equation 3.

$$AL = \frac{1{,}532}{1{,}550}\, ALM50 + T \left(1 - \frac{1{,}532}{2{,}718}\right). \qquad (3)$$

Computing the numeric value of the final term yields equation 4.

$$AL = \frac{1{,}532}{1{,}550}\, ALM50 + T\,(0.44)\,. \qquad (4)$$

Equation 4 states that the actual axial length in the pseudophakic eye can be obtained by multiplying the apparent axial length measured at 1,550 m/sec (ALM50) by the fraction (1,532/1,550), which converts to the aphakic tissue velocity, then adding 44% of the center plastic thickness of the intraocular lens. If the ultrasonic unit can be set to a tissue velocity of

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TABLE
CENTER THICKNESS OF INTRAOCULAR LENS*

LENS POWER (D)	DIAMETER OF LENS OPTIC	
	6 MM	7 MM
10	0.61	0.72
20	0.94	1.13
30	1.30	1.60

*Nominal values in millimeters for intraocular lenses made of polymethylmethacrylate.

1,532 m/sec, then the fraction becomes 1 (1,532/1,532) and actual axial length is obtained by simply adding 44% of the lens thickness to the meaured axial length using the aphakic tissue velocity. Empiric data verify these results.[4]

For example, suppose an apparent axial length in a pseudophakic eye of 22.0 mm were obtained with a tissue velocity of 1,550 m/sec with a 25-diopter intraocular lens that has a center thickness of 1.40 mm. The actual axial length would be obtained by multiplying (1,532/1,550) times 22.0 mm to get the apparent aphakic axial length (21.74 mm), then adding 44% of the 1.40-mm lens thickness (0.62 mm), yielding 22.36 mm. Notice that if the lens thickness effect had been ignored, the error would be 0.62 mm using 1,532 m/sec and 0.36 mm using 1,550 m/sec, resulting in an error of 1 to 2 diopters in the predicted refraction.

Nominal center plastic thicknesses for 6- and 7-mm optic diameter polymethylmethacrylate lenses for three dioptric powers are shown in the Table. Exact thicknesses can be obtained from the lens manufacturer and depend on optic diameter and configuration, for example, biconvex, meniscus, and convexoplano.

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Transient Comitant Esotropia in a Child With Migraine

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Diplopia is an uncommon manifestation of migraine. The syndrome of ophthalmoplegic migraine[1] is typically seen in children in whom a third nerve palsy (and rarely a sixth nerve palsy) follows the headache phase. The findings in basilar artery migraine[2] may mimic the findings in vertebrobasilar insufficiency, including diplopia.

A 10-year-old boy had recurrent headache, one of which was preceded by transient photopsias, and severe motion sickness over a several-year period, which had been diagnosed as migraine. His mother has severe common migraine and his father had had one episode of transient scintillating scotoma without headache. I examined the boy during two episodes of horizontal diplopia. The first episode lasted approximately 20 minutes. The boy had 10 prism diopters of comitant esotropia at near. He was orthophoric with distance fixation, and ocular versions were normal. Abduction saccades were grossly normal bilaterally. Results of pupil examination were normal. No deviation was evident 30 minutes later, even after an attempt to dissociate the eyes with patching. During the second episode, 1½ years later, a small comitant esotropia at both distance and near fixation occurred, which lasted 20 minutes and completely abated. Earlier that day he had suffered severe headaches necessitating analgesics and bed rest.

Although the precise cause of the aura of migraine is speculative (for example, vasospasm causing ischemia, neuronal depression), clinical anatomic localization is usually straightforward. Thus, bilateral scintillating scotoma is attributed to occipital dysfunction, ophthalmic migraine with unilateral visual loss resulting

from retinal or optic nerve involvement, and ophthalmoplegic migraine resulting from oculomotor or abducens neuropathy. However, the location of the lesion that causes a transient comitant esotropia, as demonstrated in this case, remains elusive.

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Previtreous Space Gas Sequestration During Pneumatic Retinopexy

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The use of intraocular gas has become popular in the management of selected retinal detachments and as an adjunct to scleral buckling procedures. We studied an unusual complication of gas injection, entrapment of the gas bubble in the previtreous space.

Case 1

A 62-year-old man recently had an encircling scleral buckle and radial sponge placed for a retinal detachment. The posterior edge of the break gaped and subretinal fluid extended into the macula. A gas injection was done to close the break. Standard retrobulbar anesthesia was administered and the break treated with cryopexy. A 30-gauge, ½-inch needle was inserted 3.5 mm posterior to the corneoscleral limbus. Perfluoropropane, 0.3 ml, was injected. After the needle was withdrawn, the bubble could be seen near the injection site and was noted to be relatively immobile. On the first postoperative day the gas bubble was in the same location but had expanded and was against the lens peripheral to Wieger's hyaloideocapsular ligament. It had a partial doughnut configuration. Multiple attempts at head positioning failed to dislodge the expanding bubble. Intraocular pressure was normal. The patient was taken back to the operating room on the same day and the trapped gas was removed by inserting a 30-gauge needle through the pars plana, over the bubble, and venting it to the atmosphere. Another 0.3 ml of perfluoropropane was injected without complication with the needle inserted up to the hub. The detachment was successfully repaired.

Case 2

A 30-year-old myopic woman underwent pneumatic retinopexy for repair of a primary retinal detachment. The eye was rotated to allow injection of the gas through the superior pars plana. The needle tip was observed while the gas was being injected. After injection the gas bubble failed to cross the central lens axis with forced ductions of the globe. The only movement seen was a subtle circumferential one peripheral to Wieger's hyaloideocapsular

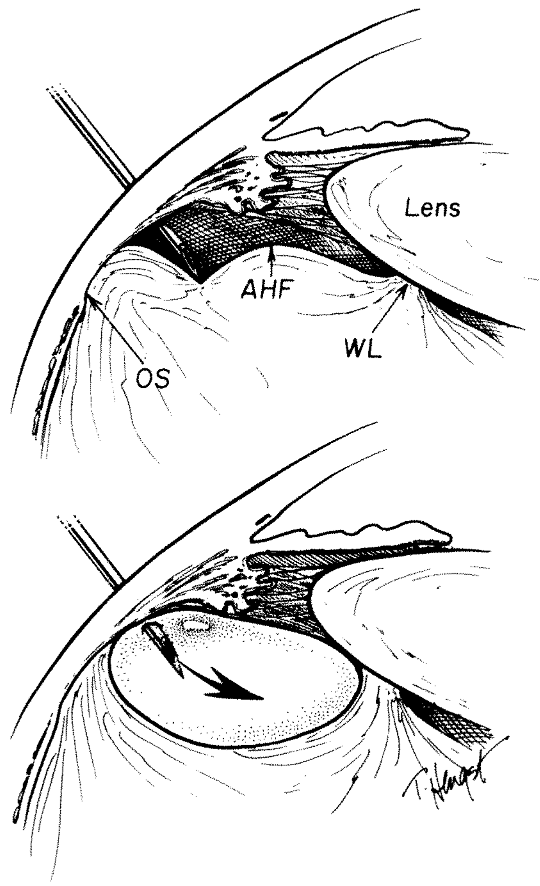

Fig. 1 (Steinmetz, Kreiger, and Sidikaro). Top, Needle inserted into the previtreous space; OS, ora serrata; AHF, anterior hyaloidal face; WL, Wieger's hyaloideocapsular ligament. Bottom, Gas bubble sequestered within the previtreous space.

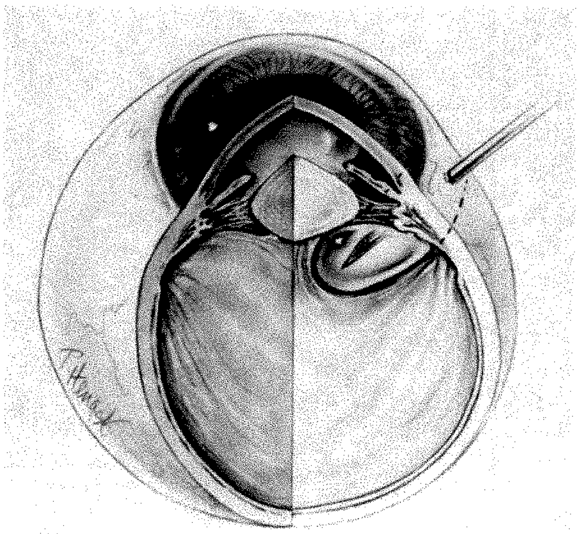

Fig. 2 (Steinmetz, Kreiger, and Sidikaro). Gas bubble trapped by the previtreous space assumes an arcuate configuration.

ligament. The gas was removed as in Case 1 and new perfluoropropane injected with the needle inserted up to its hub. The retinal detachment was repaired successfully.

Detachment of the pars plana epithelium from gas injection has been reported previously.[1] In our two cases the gas was probably trapped in the potential space between the lens and the anterior hyaloidal space (Fig. 1, bottom).

The previtreous space is bordered by the following structures: anteriorly, the anterior pars plana epithelium and pars plicata of the ciliary body, and lens zonule; centrally, Wieger's hyaloideocapsular ligament; posteriorly, the anterior hyaloidal face; and peripherally, the anterior ciliary vitreous base[2,3] (Fig. 1, top).

Failure to penetrate the anterior hyaloidal face with the injecting needle and the resultant sequestration of the gas in the previtreous space may be the result of one or a combination of factors, including a dull needle tip, an inelastic anterior hyaloidal face, and insertion of the needle tip followed by its partial withdrawal into this space before injecting to avoid creating small bubbles.

Intraoperatively this complication can be recognized by immobility of the gas bubble and failure of the gas bubble to cross the central lens axis with globe ductions. If trapped in the previtreous space the bubble will have an arcuate configuration, be immobile, or will slowly begin to circumscribe the lens peripheral to Wieger's ligament (a zone measuring approximately 8 to 9 mm in diameter)[4] (Fig. 2).

Proper treatment requires prompt recognition of the trapped gas and removal via needle aspiration. New gas can then be injected after deeper insertion of the needle into the central vitreous cavity, preferably under direct observation. If unrecognized the gas bubble trapped in this space could expand, creating retinal dialysis, lens dislocation, or cataract.

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Incidence of Corneal Crystals in the Monoclonal Gammopathies

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R. F. Brubaker, M.D.,
and P. R. Greipp, M.D.

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The monoclonal gammopathies are characterized by proliferation of a single clone of plasma cells that produce a monoclonal protein. This group of disorders includes multiple myeloma, macroglobulinemia, primary amyloidosis, monoclonal gammopathy of undetermined significance, solitary myeloma, and others.[1] Crystalline deposits can occur in the corneas of patients with these disorders, although the incidence is unknown.[2-4] Occasionally the diagnosis is first suspected on the basis

of a careful slit-lamp examination. In the past few years, we have seen two patients referred by ophthalmologists for evaluation of corneal crystals. Both patients had undiagnosed monoclonal gammopathies. To determine how commonly corneal crystals occur in patients with monoclonal gammopathy and whether slit-lamp examination might be a valuable screening procedure for these disorders, two of us (W.M.B. and R.F.B.) examined the eyes of 100 unselected patients with monoclonal gammopathies seen in the Hematology Department. All patients gave written informed consent for the examination.

None of the patients had a history of severe ocular disease or surgery. No corneal vascularization or scarring was present. Of 100 patients, 87 had monoclonal protein spikes noted on serum electrophoresis performed at the time of ocular examination (Table). The 13 patients without monoclonal protein spikes had primary systemic amyloidosis or multiple myeloma. For each eye, we recorded whether or not definite corneal crystals were present and graded the sludging of blood in the bulbar conjunctival vessels, another ocular sign of the monoclonal gammopathies.[2] The examiners did not know the patients' specific diagnoses or serum monoclonal protein concentrations.

Corneal crystals were noted in only one patient, who had fine mat-like crystals in the superficial half of the inferior two thirds of the stroma of both corneas. Both eyes had a scant, mucoid tear film and no sludging of blood in the conjunctival vessels. The patient had primary amyloidosis.

Sludging of blood in the conjunctival vessels was graded as absent (43 cases), mild (35 cases), or moderate (22 cases). In all cases, the amount of sludging was similar in both eyes. There was a positive correlation between the concentration of monoclonal protein in the blood and the amount of sludging (Spearman's rho = 0.34, P = .002), consistent with increasing blood viscosity.[5]

We found corneal crystals in only one of 100 patients with monoclonal gammopathy; therefore, slit-lamp examination is not a useful screening procedure for this systemic disorder. Although an increased serum protein concentration may be necessary for the production of corneal crystals or conjunctival vascular sludging in patients with monoclonal gammopathy, other unknown factors must also play a role.

TABLE
SERUM MONOCLONAL PROTEIN LEVELS IN STUDY PATIENTS

DIAGNOSIS	NO. OF PATIENTS WITH MONOCLONAL SPIKE/TOTAL	MEAN ± S.D. MONOCLONAL PROTEIN (G/DL)
Multiple myeloma	51/55	3.63 ± 1.77
Monoclonal gammopathy of undetermined significance	20/23	1.70 ± 0.55
Primary amyloidosis	12/17	1.10 ± 0.67
Macroglobulinemia	3/3	3.70 ± 1.21
Solitary myeloma	1/2	0.70

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Capnocytophaga Keratitis

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Joseph Frucht, M.D.,
Howard Krausz, M.D.,
and Sandy T. Feldman, M.D.
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Capnocytophaga is a gram-negative bacillus that is part of the normal human oral flora. It is frequently isolated in individuals with periodontitis or respiratory infections, and in immunocompromised hosts with sepsis.[1] Two

cases of keratitis were reported before 1985[2] and five cases were described in 1988.[3-5] We treated a patient with keratitis who responded quickly to medical treatment and had a clinical appearance suggestive of fungal keratitis.

A 35-year-old man was struck in his right eye with a foreign body while using a weed trimmer. Nine days after the injury examination disclosed a visual acuity of 20/50 in the right eye and a corneal abrasion. After 36 hours of patching, a punctate area of staining remained and a combination of dexamethasone and polymyxin B sulfate, four times a day, was begun for mild iritis. The patient returned three weeks later complaining of severe pain and decreased vision. At that time, a corneal ulcer was diagnosed. The ulcer was scraped and plated onto appropriate media for aerobic and anaerobic bacteria and fungi. The patient was admitted for treatment with fortified tobramycin and cefazolin alternating every half hour.

Because the ulcer was not healing, the patient was referred after three days to the Cornea Service. Examination showed a 3×3.2-mm corneal ulcer elevated in places with a surrounding infiltrate and an intact epithelial edge (Figure). The ulcer was rescraped and again plated onto appropriate media. Gram stain showed rare polymorphonuclear leukocytes. A fungal corneal ulcer was suspected and a regimen of natamycin every hour and commercial strength tobramycin every two hours was started. Over the next three days complete epithelialization occurred and the frequency was reduced to four times daily.

Results of the first set of cultures, obtained only after healing of the ulcer, grew *Capnocytophaga ochracea* on blood and chocolate agar kept in a microaerophilic environment as well as on *Brucella*, K_1, and Hemin anaerobic medium. The repeat set of cultures showed no growth; however, gingival cultures taken later grew *C. ochracea.*

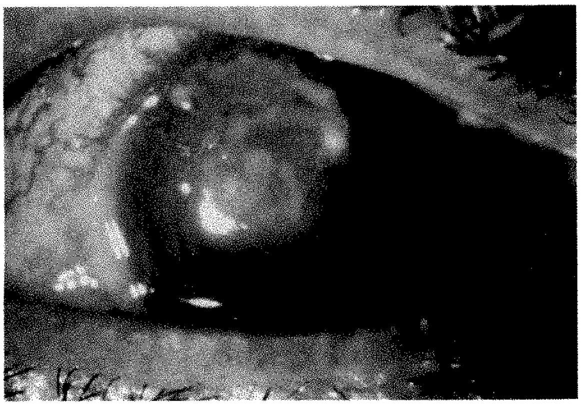

Figure (Pamel and associates). Slit-lamp photograph at 72 hours shows a gray anterior stromal ulceration surrounded by an infiltrate and a rim of healed epithelium.

Our case showed a clinical picture typically seen in fungal ulcers. The patient sustained a corneal abrasion from a foreign body and was using topical corticosteroids when he developed a delayed corneal ulcer. On culture *Capnocytophaga* was identified. This group of organisms has gliding motility, capnophilic metabolism, and exhibits fastidious growth patterns on microaerophilic and anaerobic media.[1,2] The mode of transmission was probably mouth to hand to eye, since the patient had gingivitis, which when cultured, showed this organism. The lowest 50% inhibitory concentrations were to penicillin, tetracycline, chloramphenicol and clindamycin. While only intermediate sensitivity to cefoxitin was noted, the fortified dosage and frequent regimen with cefazolin early in the course eradicated this organism within 72 hours.

Capnocytophaga ochracea keratitis can mimic not only *Acanthamoeba*[3] but a fungal corneal ulcer, and it is being recognized more frequently as a cause of keratitis. Increased awareness of this entity, of the careful microbiologic techniques necessary to identify this fastidious organism, and of the usual resistance to aminoglycosides and sometimes cephalosporins is necessary to begin treatment with the most effective antibiotics.

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Keratitis Associated With Disposable Soft Contact Lenses

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Complications of extended-wear contact lenses include infectious and noninfectious corneal ulcers, corneal edema, peripheral vascularization, and giant papillary conjunctivitis.[1] Disposable soft contact lenses were designed to reduce the complications associated with extended-wear lenses[2] by providing frequent, affordable replacements. We studied a case of keratitis associated with disposable soft contact lens wear.

A healthy 18-year-old man with no history of ocular disease had been wearing disposable soft contact lenses for five weeks. He replaced the lenses every two weeks. He developed blurred vision, pain, photophobia, and redness in his left eye after wearing his third pair for one week. He removed the left lens, but the symptoms continued tó get worse.

On examination 24 hours later, best-corrected visual acuity was L.E.: 20/50. The left eye had mild eyelid edema with protective blepharoptosis. Results of slit-lamp examination of the right eye were normal. The left eye had a moderately injected conjunctiva, and two superficial corneal infiltrates with overlying epithelial defects were present. One infiltrate was just inferior to the visual axis and measured 2 mm in diameter, and the other was near the superior corneoscleral limbus and measured 1 mm in diameter. The anterior chamber showed a trace cellular reaction. The patient denied any trauma or manipulation of his lens after its initial placement. On examination, the lens had no deposits or defects.

He was treated with fortified tobramycin, 14 mg/ml, and cefazolin, 50 mg/ml, eyedrops every hour. Over the following two weeks, the infiltrates gradually resolved leaving only a superficial scar at each site. Visual acuity returned to 20/25. Cultures from initial corneal scrapings and the contact lens did not grow bacteria or fungi.

Our case suggests that disposable soft contact lenses worn for one to two weeks may be vulnerable to some of the same complications as extended-wear lenses. We recommend close follow-up of patients who wear disposable soft contact lenses as well as careful patient education and selection. The complications of disposable soft contact lens wear are not yet established, and further studies are warranted to assess the safety of these devices.

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Spelling of Anhidrosis

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In the November issue (Am. J. Ophthalmol. 106:590, 1988), I came upon the word anhydrosis in a context that implied a sweat deficiency. This is a common misspelling of anhidrosis. The ancient Greeks clearly distinguished between sweat (*hidros*) and water (*hydōr*) in their spelling. The connecting forms of these words were *hidro-* and *hydro-*. Since we borrowed these words from them, we should be careful not to confuse them.

Most of us first encountered the word anhidrosis in medical school when were told that the signs of Horner's syndrome were "ptosis, miosis, and anhidrosis." The last two words were generally pronounced with the emphasis on the long "i": "meiosis" and "anheidrosis." I suspect they came to be pronounced this way because any triad is easier to remember if it rolls off the tongue with a rhyme and a firm meter. Triads are, after all, nothing more than mnemonic devices.

For the sake of a little jog to the memory, we have been taught to say these two words in a way that brings a wrong spelling to mind, with the result that we are still struggling to learn that miosis is not spelled meiosis, and that anhidrosis is not spelled anhydrosis.

Correspondence

Correspondence concerning recent articles or other material published in THE JOURNAL should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

Management of Anterior and Posterior Proliferative Vitreoretinopathy XLV Edward Jackson Memorial Lecture

EDITOR:

In the article "Management of anterior and posterior proliferative vitreoretinopathy. XLV Edward Jackson Memorial Lecture" (Am. J. Ophthalmol. 106:519, November 1988) by T. M. Aaberg, the author gives some cogent advice regarding management of subretinal proliferation. In cases in which retinal reattachment may be precluded by subretinal proliferative membranes, one possible approach is to remove the membranes by grasping them with a hook and pulling them anteriorly through a retinotomy. The retinotomy should be made perpendicular to the direction of the subretinal strand for most efficient removal with the smallest chance of damaging the retina or unduly enlarging the retinotomy site.

For removal of these membranes, Dr. Aaberg recommended exerting traction tangentially to the retinal surface. I believe that it would be preferable to exert this traction at an angle normal to the retinal surface rather than tangential. Normal to the retinal surface is the only force vector at which there is no component parallel to the retinal surface that could tear or enlarge the retinotomy.

ROBERT J. SCHECHTER, M.D.
Los Angeles, California

Reply

EDITOR:

I appreciate the thoughtful correspondence of Dr. Schecter regarding the removal of subretinal membranes. The incision should be parallel to the nerve fiber layer to minimize damage to the axons. I agree that initially the membrane is drawn into the vitreous cavity (as was shown in Figure 8). However, once the membrane is partially mobilized, I find the membrane can best be stripped free of these subretinal attachments with as little enlargement of the retinotomy as possible by pulling tangential to the retinal surface. If continued traction is perpendicular to the retina, the residual attachments subretinally fixate the membrane and the vector force at the retinotomy site serving to enlarge the opening.

THOMAS M. AABERG, M.D.
Atlanta, Georgia

The Development of Lacquer Cracks in Pathologic Myopia

EDITOR:

In the article "The development of lacquer cracks in pathologic myopia" by Richard M. Klein and Stuart Green (Am. J. Ophthalmol. 106:282, September 1988), the authors state that histologic examination of lacquer cracks has not been previously reported. The histopathology of lacquer cracks was reviewed by Green, W. R.: Retina. Myopia. In Spencer, W. H.: Ophthalmic Pathology. An Atlas and Textbook, ed. 3. Philadelphia, W. B. Saunders, 1985, vol. 2, chap. 8, pp. 914–920.

WILLIAM W. MILLER, M.D.
San Francisco, California

Reply

EDITOR:

We would like to thank Dr. Miller for bringing to our attention the reference on the histopathology of lacquer cracks.

RICHARD M. KLEIN, M.D.
New York, New York
STUART GREEN, M.D.
Piscataway, New Jersey

BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Ocular Motility. By Virginia Carlson Hansen. Thorofare, New Jersey, Slack Inc., 1988. Softcover, 127 pages, index, illustrated. $30

Reviewed by M. L. MAZOW
Houston, Texas

This book is one of a series specifically written for ophthalmic technologists and assistants. In the preface, the author expresses the hope that this book will change opinions about ocular motility and "transform its frustrations into challenges."

The reader is led through the techniques of the examination and is shown how careful history taking can narrow the differential diagnosis and thus change the sequence of the tests in the examination. The role of the ophthalmic medical assistant in patient care is also explored.

There are a few problems. Putting quick summaries in the margins of the pages is a good idea, but when placed on the wrong page, they only frustrate the reader. Sometimes specialized words like "saccade" or "electromyography" are thrown in without explanation or definition. The section on amblyopia, although thorough, fails to include the currently recommended patching regimen for children under 1 year of age.

This book does, however, provide the basic information for a fundamental understanding of strabismus and for the evaluation, work-up, and management of motility problems by the ophthalmic medical technologist. I applaud Ms. Hansen for helping to make this material available.

Retinopathy of Prematurity. Problem and Challenge. Edited by John T. Flynn and Dale L. Phelps. New York, Alan R. Liss, Inc., 1988. 345 pages, index, illustrated. $140

Reviewed by RON V. KEECH
Iowa City, Iowa

This book is based on the proceedings of a symposium on retinopathy of prematurity held at the National Institutes of Health in 1985 and has come to press without mention of the recently published preliminary findings of the Multicenter Trial of Cryotherapy for Retinopathy of Prematurity. It is nevertheless the best available overview of the condition, of the basic research being done, of the pathophysiologic mechanisms, and of the controversies in the management of retinopathy of prematurity.

The clinician will find in this book discussion of diagnostic techniques, the classification of the disease, and various treatment approaches such as cryopexy, scleral buckling, and vitrectomy. Long-term ocular problems such as refractive error, amblyopia, and glaucoma are also discussed. Any ophthalmologist with an interest in this condition should own a copy of this book.

The Mathematical Tourist. By Ivars Peterson. New York, W. H. Freeman and Company, 1988. 240 pages, index, illustrated. $17.95

Reviewed by FRANK W. NEWELL
Chicago, Illinois

This is a popularization of modern mathematics that explores many of the intriguing puzzles in the field: proof that four colors are enough to fill every conceivable map that can be drawn on a flat sheet of paper so that no country sharing a common boundary has the same color; the mathematical basis of computed tomography, modern cryptography, prime numbers, and factoring, and so on through knots, soap bubbles, the fourth dimension, chaos, and many other topics of mathematical interest. This volume is for those of us who are awed by the questions asked by modern mathematicians and baffled by their methods.

Books Received

AFB Directory of Services for Blind and Visually Impaired Persons in the United States, ed. 23. By American Foundation for the Blind. New York, American Foundation for the Blind, Inc. 378 pages, index, soft cover. $39.95

This directory lists low-vision clinics, state commissions for the blind, vocational rehabili-

tation agencies, employment training programs, talking book and braille libraries, dog guide schools and services, and much more. Clear explanations are given of how to obtain these services. It is a valuable reference work.

Basic Refraction Techniques. By David D. Michaels. New York, Raven Press, 1988. 188 pages, index, illustrated. $31.50

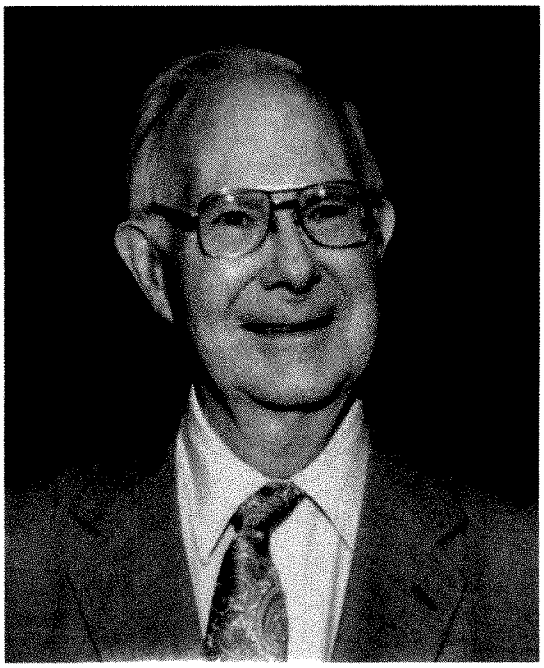
A step-by-step manual consisting chiefly of material distilled from the author's 1985 textbook. A good starting place for the novice.

Molecular Biology of the Eye. Genes, Vision, and Ocular Disease. UCLA Symposium on Molecular and Cellular Biology, New Series, vol. 88. Edited by Joram Piatgorsky, Toshimichi Shinohara, and Peggy S. Zelenka. New York, Alan R. Liss, Inc., 1988. 471 pages, index, illustrated. $95

Anyone interested in the molecular mechanisms of the eye and its diseases will find this collection of 45 papers valuable and stimulating. It represents the current state-of-the-art of molecular ophthalmology.

Obituary

PLACIDUS JOSEPH LEINFELDER
1905–1988



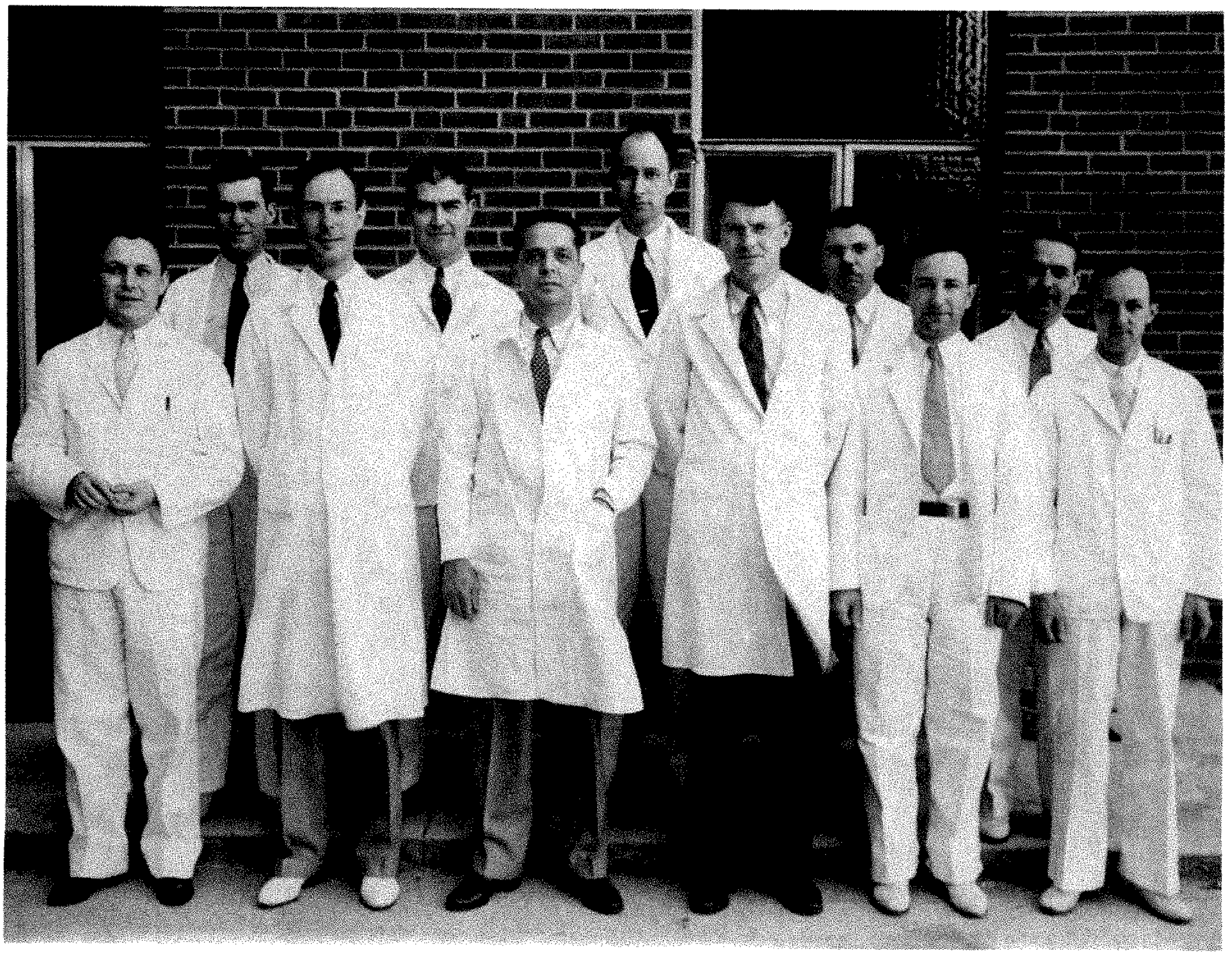
Placidus Joseph Leinfelder
1905–1988

Placidus Joseph Leinfelder, professor emeritus of ophthalmology at the University of Iowa, and known throughout his life as "P.J.," died Nov. 9, 1988, at the age of 83.

P.J. had been associated with the Department of Ophthalmology for many years. Born and raised in LaCrosse, Wisconsin, he earned his B.A. and M.D. degrees and completed his internship at the University of Wisconsin, then came to Iowa in 1930 to be one of C. S. O'Brien's ophthalmology residents. He joined the faculty as an instructor in 1934 and became full professor in 1946. When he retired in 1973, he had been seeing eye patients in the department and doing three to five cataract extractions most Friday mornings for longer than anyone else in the department could remember.

P.J. didn't call himself a neuro-ophthalmologist, but that was clearly where his interests lay. This was acknowledged by O'Brien in 1938 when P.J. was named the head of a neuro-ophthalmology section in the department. P.J.'s American Ophthalmological Society thesis, accepted in 1938, was on "Retrograde degeneration in the retina and optic nerves." He gave courses at the Academy on neuro-ophthalmic topics from 1937 to 1969. During the same years his talks to various midwest state medical societies resulted in publications such as "Papilledema and optic neuritis," "Misconceptions in neuro-ophthalmology," "Why test visual fields?," "The diagnosis and treatment of ocular neuroses," and "The diagnostic significance of some ocular complaints."

Some of P.J.'s earliest investigative work was in biochemistry (with Peter Salit) and on roentgen-ray cataracts (with H. D. Kerr), and these two subjects came together for him 20 years later in a series of papers on the metabolism of the crystaline lens and on experimentally produced radiation cataracts. This, in turn, led to a period of service on the Advisory Committee to the Atomic Bomb Casualty Commission.



The faculty and residents of the Department of Ophthalmology at the University of Iowa in 1936. Front row, left to right: Alson E. Braley, P. J. Leinfelder, Cecil Starling O'Brien, Phillips Thygeson, Carl A. Noe, William Lanou. Back row, left to right: Ralph H. Gilbert, Erwin W. Newman, Maynard A. Wood, James H. Allen, Jacob F. Schultz.

He retired at age 68, but he stayed in the department part-time for another five years, taking care of some of his old patients who had known no other ophthalmologist for 30 to 40 years, making himself available to the residents, and serving as the voice of experience at department faculty meetings. It was gracefully done. He was a model for all retiring professors —wise, alert, ready with sound advice but not offering it until it became perfectly clear that all of us young fools were going to keep blathering along without ever getting to the heart of the problem. He was kind, avuncular, and approachable, and during those years he earned our deepest respect for his knowledge, his clinical wisdom, and his humanity. We still miss him.

H. STANLEY THOMPSON

Meetings

OCULAR MICROBIOLOGY AND IMMUNOLOGY GROUP: 22nd ANNUAL MEETING

The 22nd annual meeting of the Ocular Microbiology and Immunology Group was held Oct. 7, 1988 at the Riviera Hotel in Las Vegas.

R. H. S. Langston and D. M. Meisler described six cases of infectious crystalline keratopathy. They noted that these cases and 16 other cases from the literature were caused by *Streptococcus viridans* and other organisms such as *S. mitans*, *Staphylococcus aureus*, and *Candida*.

Many patients had underlying herpes simplex keratitis and had been treated with intensive topical corticosteroids. They mentioned that crystalline keratopathy was difficult to manage by medical therapy alone, and that debridement or therapeutic keratoplasty was often necessary.

T. O'Brien, M. Sawusch, S. Updegraff, J. Dick, and J. Gottsch compared topical therapy of methicillin-resistant *St. epidermidis* with cefazolin, cefazolin plus tobramycin, vancomycin, and ciprofloxacin in a rabbit model. Treatment with ciprofloxacin and vancomycin resulted in a significant reduction in bacterial counts compared with the other antibiotics.

D. F. Goodman and J. D. Gottsch reported two cases of methicillin- and gentamicin-resistant *St. epidermidis* treated successfully with topical vancomycin.

C. Newton described a 24-year-old contact lens wearer who developed bacterial keratitis caused by *Bacteroides gingivalis*. The patient denied putting the contact lenses in his mouth, but was using distilled water to clean his lenses. The organism was sensitive to an entire panel of antibiotics except metronidazole.

J. Robin, R. Chan, M. Jackson, and A. Y. Matoba described the use of fluorescein-conjugated lectins for the visualization of mycobacteria. Concanavalin A and wheat germ agglutinin produced the brightest degree of organism fluorescence, and these glycoproteins can be used to stain many other classes of organisms.

S. Holland, S. Pflugfelder, D. Miller, and G. Rosenwasser described a 35-year-old extended-wear soft contact lens wearer who developed an *St. aureus* corneal ulcer and extensive necrotizing scleritis. *Pseudomonas aeruginosa* was cultured from the sclera and after enucleation, both *P. aeruginosa* and *Bacillus cereus* were cultured from the sclera. The patient was found to be lymphopenic and seropositive for human immunodeficiency virus (HIV). They suggested that bacterial ocular infections may be more severe in HIV-infected individuals.

S. D. Schwartz, R. B. Phinney, D. A. Lee, and B. J. Mondino described the use of therapeutic collagen shields to release gentamicin and vancomycin individually or in combination. The shields were presoaked with the antibiotic and placed in rabbit eyes. Most of the antibiotic was released during the first 30 minutes (for gentamicin) and the first six hours (for vancomycin). Antibiotic levels in the tears, cornea, and aqueous humor were comparable or higher than those achieved by drop therapy.

J. J. Reidy, B. M. Gebhardt, K. Padumane, and H. E. Kaufman described the ocular pharmacokinetics of cyclosporine delivered by collagen corneal shields. The shields were presoaked with cyclosporine and placed on rabbit eyes. Cyclosporine levels were higher in the cornea and aqueous humor than levels achieved by cyclosporine eyedrops.

R. W. Snyder, R. A. Hyndiuk, S. B. Koenig, and M. L. McDermott described continuous delivery of antibiotic with a miniature portable medication pump. The antibiotic was delivered to the eye through a thin, flexible Silastic tube. The authors have treated severe bacterial keratitis with this technique and believe it has advantages over other types of antibiotic delivery.

P. A. Asbell, P. J. Sakol, and Y. S. Sang described a case of *Candida* keratitis after penetrating keratoplasty. The organism was cultured from the donor cornea at the time of surgery. Treatment consisted of topical natamycin and miconazole, and oral ketoconazole. This case, and others described in the literature, are extremely difficult to treat and the authors believed that removal of the graft early might be helpful. They also raised the question of whether an antifungal medication should be added to the eyebank culture medium.

D. O'Day, G. Foulds, R. Robinson, T. Williams, and S. Head described the accumulation of fluconazole in the rabbit cornea after oral administration of the drug. This water-soluble antifungal agent showed excellent oral absorption, good penetration into the rabbit eye, good activity against fungal organisms, and few side effects. They recommended divided doses rather than a single dose, and because the drug is a static drug, they believe long-term therapy will be necessary.

J. H. Brinser and L. R. Groden reviewed 168 patients from whom *Bacillus* species were isolated from ocular sources. Eighty-eight percent were isolated from the eyelids or conjunctiva, and organisms were most sensitive to aminoglycosides and vancomycin.

W. T. Driebe, G. A. Stern, R. Epstein, and G. S. Visvesvara described a potential role for topical clotrimazole in the treatment of *Acanthamoeba* keratitis. In two patients who failed conventional therapy including multiple antiamebic medications, clotrimazole was successful in controlling recurrent infection after penetrating keratoplasty. Three other patients had an excellent response to medical therapy when clotrimazole and other anti-ameba agents (pro-

pamidine isethionate and neomycin sulfate-polymyxin B sulfate-gramicidin) were used. Clotrimazole 1% suspension formulated in artificial tears or commercially available clotrimazole cream were used.

M. S. Osato, S. Wong, K. R. Wilhelmus, and D. B. Jones found ciclopirox olamine, a pyridone antifungal agent that adversely affects cellular metabolism in susceptible fungi, to be a potentially useful medication for the treatment of amebic keratitis. The drug was effective in treating amebic keratitis in rabbits.

T. Rabinovitch, S. S. Weissman, H. B. Ostler, J. D. Sheppard, D. N. Skorich, and R. Biswell discussed the diagnostic signs and symptoms of *Acanthamoeba* keratitis and its therapeutic options. Pain was out of proportion to the corneal findings and correlated with radial neurokeratitis. Corneal sensation was decreased or absent in most cases and most were culture positive. Corticosteroid treatment led to a greater delay in diagnosis and an inevitable surgical form of treatment.

M. Cobo, A. Proia, and G. Klintworth described a case of "pseudoacanthamoeba" keratitis. They suggest that *Acanthamoeba* keratitis may be overdiagnosed and mistaken for other entities such as herpes simplex keratitis. They stated that visualization of the organism on the biopsy specimen was not sufficient evidence for infection and that cultures were necessary to make a firm diagnosis.

G. O. D. Rosenwasser, S. P. Holland, S. C. Pflugfelder, and M. Lugo described three patients with keratitis related to topical anesthetic abuse. All cases were initially diagnosed as *Acanthamoeba*, but cultures were uniformly negative.

C. M. Kirkness and L. A. Ficker described the role of penetrating keratoplasty in the management of acute suppurative keratitis. A wide range of infecting organisms was found, although *Streptococci* were the most common (22%). Corneal transplants were performed in 21 eyes and nine achieved a final visual acuity of 20/60 or better. Failure was the result of graft rejection or persistent infection. Despite these complications, the authors believed the results were encouraging when grafts were needed to save the eye.

M. Mannis, J. Cullar, C. Murphy, M. Selsted, and T. Reid described the use of defensins for the eradication of ocular pathogens in vitro. Defensins are small antimicrobial peptides that have been isolated from macrophages and neutrophils. They are major components of the oxygen-independent microbial killing pathway. They are effective in vitro against a wide variety of ocular pathogens. Defensins present potent new antimicrobial agents that may also promote wound healing.

J. D. Sheppard, J. Schachter, C. R. Dawson, P. Courtright, J. Moncada, and A. Lorincz described the use of DNA probes to identify *Chlamydia* in conjunctival smears. Organisms could be identified by the DNA probe as well as by MicroTrak direct fluorescent antibody, Chlamydiazyme enzyme immunoassay, Giemsa cytology, and cell culture isolation. Isolation of the organisms by culture may be difficult because of possible *Chlamydia* growth arrest by lymphokines.

T. Roussel, S. Pflugfelder, E. R. Olson, T. Rice, D. Meisler, G. Hall, and D. Miller described delayed onset, chronic postoperative endophthalmitis associated with *Actinomyces* species in four patients. This gram-positive, nonspore-forming anaerobic bacillus produced a clinical picture similar to that of *Propionibacterium acnes*, and all cases responded to intraocular, topical, and systemic antibiotic therapy as well as pars plana vitrectomy and partial iridectomy. The authors emphasized the need to perform anaerobic cultures in all unexpected cases of chronic postoperative inflammation.

S. K. Wong, D. M. Meisler, H. B. Cohen, Z. N. Zakov, and G. Hall described chronic infectious endophthalmitis after cataract surgery and lens implantation caused by *P. acnes* and *Candida parapsilosis*. The authors believed that low virulent organisms such as these produce similar clinical features, including an indolent course with late onset intraocular inflammation, granulomatous iridocyclitis, and a plaque on the posterior capsule.

S. A. F. Al-Hazzaa and J. A. Gammon described a case of *Serratia marcescens* endophthalmitis in a newborn infant. This gram-negative bacillus may have been a hospital-acquired organism since the baby was ill from birth and had an umbilical artery catheter.

J. Baum, M. Barza, and E. Lynch described the vitreal pharmacokinetics of third-generation cephalosporins in rabbits. These agents, particularly cefepime, have advantageous pharmacokinetic properties after intravitreal injection, but are likely to have little value when administered subconjunctivally.

G. A. Stern, M. Adi, J. Hines, J. Silbiger, S. Goldey, and Z. S. Zam reported further results of their studies on bacterial endophthalmitis in the rabbit. They showed that in a "late treatment" model, a single intravitreal antibiotic injection does not decrease the intravitreal con-

centration of bacteria over untreated controls. However, the use of repetitive intravitreal antibiotic injections does significantly reduce the number of intravitreal organisms. Also, vitrectomy combined with a single intravitreal antibiotic injection was more effective in reducing the concentration of bacteria than a single intravitreal injection alone.

M. L. Coats and G. A. Peyman investigated the effects of intravitreal amphotericin B with and without dexamethasone in exogenous fungal endophthalmitis in the rabbit. They concluded that the addition of corticosteroids promotes clearance of the destructive inflammatory process. There was no evidence that corticosteroids enhance fungal replication.

A. A. Bialasiewicz described a 25-year-old patient with acute borreliosis (Lyme disease) who had papilledema, retinal perivasculitis, and demyelinating lesions. The patient improved and antibody titers for Lyme disease decreased after treatment with tetracycline and corticosteroids.

R. P. Kowalski and Y. J. Gordon compared four different rapid diagnostic tests for ocular herpes simplex. They concluded that there is no ideal rapid direct test for herpes at the present time and that clinical examination remains the primary criterion for diagnosis of herpetic infection and the initiation of antiviral therapy.

J. Colin, F. Malet, C. Bodin, and C. Bonne described the effect of nonsteroidal anti-inflammatory agents on herpes simplex keratitis. Unlike corticosteroids, the nonsteroidal anti-inflammatory agents did not enhance ocular herpes infection.

C. F. Beyer, J. J. Reidy, J. M. Hill, and H. E. Kaufman showed that topical trifluridine reduces viral shedding and corneal lesions in reactivated herpes type 1 infection induced by intravenous cyclophosphamide and dexamethasone. The results suggest that prophylactic treatment with trifluridine can reduce the incidence and severity of a recurrent epithelial keratitis.

M. P. Langford, J. A. Colacino, S. B. Mahjoub, and J. P. Ganley described the biochemical and biological properties of a retinovirulent herpes simplex type 2 virus. The retinovirulent herpes virus exhibited similar deoxypurimidine kinase activity and an interferon sensitivity similar to herpes simplex type 1 in vitro, while being more related antigenically and biochemically to herpes simplex type 2.

Y. Centifanto and E. Porretta described genomic differences in different isolates of type 1 herpes simplex virus. Analysis of the DNA of closely related viral strains can be used to identify those regions responsible for the different disease manifestations in ocular disease.

S. Pflugfelder, S. G. Tseng, J. Pepose, M. A. Fletcher, R. L. Font, and G. Pearson proposed a chronic viral infection as a possible cause for aqueous tear deficiency. In 38 tear-deficient patients they found decreased numbers of total lymphocytes and T helper cells, depressed cell-mediated immunity, and polyclonal B cell activation. Epstein-Barr virus or cytomegalovirus could be responsible for the chronic viral infection.

J. E. Sutphin and J. B. Ward described corneal complications of Epstein-Barr virus infections in two cases. Ring-shaped or nummular infiltrates were present and serologic studies were important in making a diagnosis.

M. Nanda, V. T. Curtin, J. Hilliard, N. Bernstein, and R. D. Dix described retinitis associated with herpes B virus infection. The patient was a 37-year-old laboratory technician who sustained a penetrating wound fron a rhesus monkey and died from a progressive ascending encephalomyelitis. Vitreous cultures from both eyes and retinal cultures from the right eye were positive for *Herpesvirus simiae*. One eye had multifocal, necrotizing retinitis, panuveitis, vitritis, and optic neuritis. This was the first histopathologic examination of an eye from a patient who developed a fatal herpes B virus infection.

M. H. Friedlaender, J. Sweet, and P. Stein described a human model of allergic conjunctivitis. Cat dander was instilled in the eyes of allergic patients to elicit an immediate conjunctival inflammatory response. The allergen dose needed to produce a moderate conjunctival response was 30,000 to 50,000 times greater than the amount of allergen needed to produce a moderate skin reaction. Neutrophils were the predominant cell in conjunctival scrapings; however, eosinophils were also prominent.

S. Bonini, S. Bonini, M. G. Bucci, A. Berruto, M. Centofanti, M. Schiavone, and M. R. Allansmith described the clinical and cellular events following allergen challenge in human hay fever. They performed conjunctival provocation tests using rye grass allergen. The tear fluid cytology showed an increase of inflammatory cells, especially neutrophils and eosinophils. The cellular inflammatory reaction remained increased for 24 hours. They noted that such allergic reactions may be prolonged rather than biphasic.

S. I. Butrus, K. I. Ochsner, M. B. Abelson,

and L. B. Schwartz detected tryptase in tears after allergen conjunctival provocation, topical application of compound 48/80, and two minutes after eye-knuckle rubbing. The allergen-induced rise in tryptase was attenuated in two of five patients pretreated with cromolyn. Tear tryptase may be used as a specific marker for mast cell-dependent events and for evaluating different mast cell stabilizing agents.

M. C. Calonge, R. M. Briggs, M. R. Allansmith, and K. J. Bloch compared a passive and active model of ocular anaphylaxis in the guinea pig. In the passive model, guinea pigs were injected subconjunctivally with guinea pig anti-DNP-BGG antiserum rich in IgG-1 antibodies. Fourteen hours later, both eyes were challenged topically with di-DNP-lysine. For the active model, guinea pigs were injected with DNP-BGG emulsified in complete Freund's adjuvant. Thirty days later, one eye was challenged with di-DNP-lysine. Immediately before challenge, guinea pigs were injected intravenously with 1% Evans blue dye. After 30 minutes, conjunctival and periorbital edema and bluing were recorded and ocular tissues were weighted. The clinical responses of passive and active models were similar. However, the eyelids and conjunctiva of the passive group contained more blue dye.

A. Leonardi, R. M. Briggs, K. J. Bloch, and M. R. Allansmith described the histologic changes in ocular tissues undergoing early and late phase anaphylactic reactions. The late phase reaction occurred six to 12 hours after the immediate reaction in the guinea pig. Mast cell degranulation was prominent in the early phase, while neutrophil, eosinophil, and basophil accumulation were more marked in the late phase.

S. J. Weissman, N. Hussein, T. Rabinovitch, and H. B. Ostler described the conjunctival sequelae of graft vs host disease. This condition followed bone marrow transplantation in three patients and was characterized by cicatrizing conjunctivitis, conjunctival keratinization, symblepharon, and lower palpebral conjunctival ulcerations. Topical retinoic acid appears promising for symptomatic relief.

S. B. Mahjoub, Y.-K. Au, R. P. Misra, J. P. Ganley, and M. P. Landford described Ia antigen expression by corneal endothelial cells during allograft rejection in the rabbit. The Ia antigen expression occurred at the leading edge of the rejection and may have been related to interferon stimulation.

G. W. Zaidman described a patient who developed uveitis and siderosis from a small metallic foreign body on the peripheral iris. The patient had had a penetrating injury to the eye 32 years earlier and had no pain and discomfort in the eye until the uveitis developed. Removal of the foreign body led to rapid resolution of the uveitis, but the patient developed decreased vision related to corneal edema and cataract formation.

D. Seal, L. Ficker, and P. Wright tested 70 patients with staphylococcal blepharitis for delayed hypersensitivity to staphylococcal antigens. Relatively few patients showed delayed hypersensitivity responses to *Staphylococcus*.

E. J. Holland, C.-C. Chan, A. G. Palestine, J. J. Rowsey, and R. B. Nussenblatt described two patients with ligneous conjunctivitis who responded to treatment with cyclosporine eyedrops. Use of a 2% solution over several months resulted in complete resolution in one patient and slower recurrences in the other patient.

S. Tuft, D. Seal, M. Kemeny, and R. Buckley postulated that the origin of inflammation in atopic keratoconjunctivitis was related to staphylococcal protein A on the conjunctival mucosa which could activate inflammatory cells. Atopic patients had heavy colonization of *Staphylococcus* on their eyelids and conjunctiva. There was no specific connection to IgE. However, *Staphylococcus* or related toxins could play an etiologic role.

MITCHELL H. FRIEDLAENDER

ABSTRACT DEPARTMENT

Edited by David Shoch, M.D.

British Journal of Ophthalmology

The consensual ophthalmotonic reaction. Gibbens, M. V. (Dept. Ophthalmol., St. Thomas's Hosp., London, England SE1 7EH). Br. J. Ophthalmol. 72:746, 1988.

The ophthalmotonic reaction is defined as a pressure change in the contralateral eye when one eye only is being treated with a pressure lowering drug. To evaluate this response, the authors treated 13 normal and 13 ocular hypertensive patients with timolol, pilocarpine, and epinephrine. In the hypertensive group, there was a consensual fall in intraocular pressure for all drugs tested. In the normotensive group, a significant consensual drop in pressure was seen only with timolol. The obvious, but not fully supported, explanation is that there is systemic absorption of the drug that affects the fellow eye. Therefore, the untreated eye may not be a good control to determine whether a drug is effective. (2 figures, 3 tables, 19 references)—David Shoch

Long-term follow-up of a prospective trial of argon laser photocoagulation in the treatment of central serous retinopathy. Ficker, L., Vafidis, G., While, A., and Leaver, P. (Professorial Unit, Moorfields Eye Hosp., City Rd., London, England EC1V 2PD). Br. J. Ophthalmol. 72:829, 1988.

In a prospective randomised trial of argon laser photocoagulation in the management of central serous retinopathy, long-term follow-up (6.4 to 12.1 years) revealed no evidence that treatment significantly influenced the visual outcome as measured by the Snellen chart and by the Farnsworth-Munsell 100-hue test. Treatment did not reduce either the recurrence rate or the prevalence of chronic disease. Complications of treatment were uncommon. The justification for argon laser photocoagulation appears to be limited to the hastening of symptomatic relief by earlier resolution of serous detachment. (4 figures, 23 references)—Authors' abstract

Photocoagulation of raised new vessels by long-duration low-energy argon laser photocoagulation. A preliminary study. Zeki, S. M., and Dutton, G. N. (Tennent Inst. Ophthalmol., Univ. Glasgow, Western Infirm., Glasgow, Scotland G11 6NT). Br. J. Ophthalmol. 72:837, 1988.

A 29-year-old man with Eale's disease, in whom repeated photocoagulation of the ischemic retina failed to reduce the neovascularization, was treated at two adjacent points along the feeder vessels with 0.15 W and a 50-μm spot size delivered continuously for 30 seconds. Because this caused a small hemorrhage, a power setting of 0.1 W with a duration of 60 seconds was used. Within four days, the vessels had closed and after six months no new vessels were seen. Long-duration, low-energy burns apparently heat the vessels slowly and thus reduce the danger of disruption. (5 figures, 15 references)—David Shoch

European Journal of Cancer and Clinical Oncology

Immunocytochemical parameters in ocular malignant melanoma. Beckenkamp, G., Schafer, H., and Von Domarus, D. (Augenklinik der Universität, Martinistr, 52, D-2000 Hamburg 20, West Germany). Eur. J. Cancer Clin. Oncol. 24:S41, 1988.

In a study of a broad spectrum of immunocytochemical markers in 41 patients with melanomas, 16 specimens were obtained from patients with ocular and cutaneous nevi and 25 from those with malignant melanomas. In contrast to cutaneous and conjunctival melano-

mas, intraocular melanomas contained only small amounts of S-100 protein, which is therefore unreliable as a marker for intraocular tumors. The most useful antibody was HMB-45, which clearly marked cutaneous and ocular melanomas. It was highly specific for melanoma cells and was negative for ocular melanocytes. It was particularly suitable for identifying isolated melanoma cells. (2 figures, 2 tables, 5 references)—David Shoch

Journal of Infection

Optic neuropathy in *Borrelia* infection. Gustafson, R., Svenungsson, B., and Unosson-Hallnas, K. (Dept. Infect. Dis., Roslagstull Hosp., Stockholm, Sweden). J. Infect. 17:187, 1988.

A patient, who lived in Sweden, had a positive serologic test for the spirochete *Borrelia*. He was treated with benzylpenicillin. Approximately five months after the onset of symptoms and approximately one month after treatment, the patient developed a sudden loss of vision in his left eye. Despite corticosteroid therapy, visual acuity gradually fell to light perception and he began to lose vision in the right eye. There was no other evidence of neurologic or vascular disease. This may have been a direct result of invasion of the optic nerve by the spirochete or perhaps an immunomediated inflammation. (3 references)—David Shoch

Journal of Inherited Metabolic Disease

A closer look at the eye in homocystinuria. A screened population. Burke, J. P., O'Keefe, M., Bowell, R., and Naughten, E. R. (Dept. Ophthalmol., Metabolic Unit, Children's Hosp., Temple St., Dublin 1, Ireland). J. Inher. Metab. Dis. 11:237, 1988.

Nineteen patients had homocystinuria characterized by a deficiency in cystathionine-beta-synthetase. In fourteen of the patients a low methionine diet and massive doses of pyridoxine were begun at an average age of 22 days. The five remaining patients did not begin treatment until an average age of almost 40 years. In Group 1, two patients were severely myopic, but no patient had ectopia lentis. In Group 2, three of the five patients had ectopia lentis when examined and the other two developed dislocated lenses during the follow-up period. Although this series is small, it seems to indicate that prompt diagnosis at an early age and institution of appropriate dietary and vitamin therapy may prevent or at least delay the onset of ectopia lentis. (1 figure, 6 references)—David Shoch

Neurology

Electrophysiology versus psychophysics in the detection of visual loss in pseudotumor cerebri. Verplanck, M., Kaufman, D. I., Parsons, T., Yedavally, S., and Kokinakis, D. (B-309 West Fee Hall, Michigan State Univ., East Lansing, MI 48824). Neurology 38:1789, 1988.

The authors examined 15 women with pseudotumor cerebri using Goldmann visual fields, contrast sensitivity studies, and visual-evoked potentials to document visual loss at an early stage. The findings were compared to those in a group of 45 women who had no neurologic or ocular disease. In women with pseudotumor cerebri, 13 of 30 eyes had abnormal visual fields and 18 eyes had abnormal contrast sensitivity. The visual-evoked potential was abnormal in only five eyes. In nine eyes, the visual loss was detected only by contrast sensitivity. In five eyes, the only abnormal finding was in perimetry and only in one eye was the visual-evoked potential the sole abnormality. The authors concluded that the basic test for the presence of pseudotumor cerebri is Goldmann visual field testing, but that contrast sensitivity studies are a valuable adjunct; the visual-evoked potential is rarely useful. (2 figures, 3 tables, 12 references)—David Shoch

Neuroscience Letters

Intraretinal transplantation of fluorescently labeled retinal cell suspensions. Del Cerro, M., Notter, M. F. D., Wiegand, S. J., Jiang, L. Q., and del Cerro, C. (Dept. Neurobiol. and Anat., Univ. Rochester, School of Med., Rochester, NY 14642). Neurosci. Lett. 92:21, 1988.

The authors successfully transplanted retinal cells after dissociating them and placing them in suspension. Neuroretinal cells were taken from normal neonatal rats and transplanted into the retinas of adult normal rats or rats affected by phototoxic retinopathy. The eyes were enucleated at ten, 30, or 100 days and the cells were examined for viability. The cells, which had been previously labeled with fluorescein, had survived the dissociation and were integrated into the host retinas. The transplants were viable both in the normal retinas and in the retinas with phototoxic retinopathy. (4 figures, 17 references)—David Shoch

New England Journal of Medicine

Effect of ultraviolet radiation on cataract formation. Taylor, H. R., West, S. K., Rosenthal, F. S., Munoz, B., Newland, H. S., Abbey, H., and Emmett, E. A. (Wilmer Inst., 600 N. Wolfe St., Baltimore, MD 21205). N. Engl. J. Med. 319:1429, 1988.

This epidemiologic study was based on the exposure of 838 Chesapeake Bay watermen to sunlight. The total exposure to sunlight was calculated and the eyes were examined for the presence or absence of cataract. Approximately 40% of the men had cataracts; 27% were nuclear and 13% were cortical. The degree of opacification was then correlated with the total exposure to sunlight over the years from age 16 years. Cumulative levels of ultraviolet B significantly increased the risk of cortical cataract. There was no association between nuclear cataracts and either ultraviolet B or ultraviolet A exposure. The use of aspirin, considering both duration and dose, had no effect on the opacities. The authors also found that ordinary plastic lenses reduced the transmission of ultraviolet B to about 5%. (3 figures, 2 tables, 36 references)—David Shoch

Review of Infectious Diseases

Treatment of cytomegalovirus retinitis in patients with AIDS. Mills, J., Jacobson, M. A., O'Donnell, J. J., Cederberg, D., and Holland, G. N. (San Francisco Gen. Hosp., Bldg. 80, Ward 84, 995 Potrero St., San Francisco, CA 94110). Rev. Infect. Dis. 10: S522, 1988.

A common complication of AIDS is cytomegalovirus infection, which is usually seen in the form of retinitis. If untreated, this retinitis progresses to blindness. The only drug that thus far has been successful for the treatment of cytomegalic retinitis is ganciclovir, given intravenously in two or three divided doses. The viremia and shedding of virus from other sites is altered or reduced. However, the drug does not cure the disease and reactivation of infection and retinitis usually occurs when the ganciclovir treatments stop. Therefore it is necessary to continue treatment, with the drug administered usually as a single intravenous dose daily. This therapy delays but does not prevent reactivation of infection. Unfortunately, the drug can only be given intravenously and is not effective with oral administration. (1 figure, 23 references)—David Shoch

Science

Growth and transparency in the lens, an epithelial tissue, stimulated by pulses of PDGF. Brewitt, B., and Clark, J. I. (Dept. Biol. Structure, University of Washington, School of Medicine, Seattle, WA 98195). Science 241:777, 1988.

The authors devised a lens culture system in which they could expose the lens to various growth factors. They found that the lens does not grow steadily but rather that the growth rate varies with intermittent spurts. The lenses also developed normally when they were exposed to pulses of platelet-derived growth fac-

tor, which has been found in the aqueous humor. If the lens was exposed to this growth factor continuously or if the growth factor was absent, the lenses stopped growing, soluble proteins were lost, and cataracts formed. (3 figures, 23 references)—David Shoch

Hyperthermia protects against light damage in the rat retina. Barbe, M. F., Tytell, M., Gower, D. J., and Welch, W. J. (Dept. Anatomy, Med. College of Pennsylvania, Philadelphia, PA 19144). Science 241:1817, 1988.

Increasing body temperature in many organisms produces an increase in a family of heat shock proteins that apparently protect the organism against further damage. To test whether this is true for the central nervous system, the authors used the retina as a model for central nervous system injury. They produced the injury by exposing the retina to a standard amount of light to produce a standard injury. Two groups of rats were exposed to light damage to the retina, one group being made hyperthermic and the other acting as a control. There was a marked decrease in photoreceptor degeneration in the hyperthermic group after exposure to the test light as compared to the controls. There was also an increase in the synthesis of heat shock proteins in the retina. The authors hypothesized that these results can be extrapolated to the central nervous system generally and that a physiologic rise in body temperature may be protective by increasing heat shock protein production. (4 figures, 28 references)—David Shoch

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The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length. Announcements of meetings and courses must be received at least four months before the event.

Minnesota Academy of Ophthalmology: Twentieth Annual William L. Benedict Lecture

The Minnesota Academy of Ophthalmology presented the Twentieth Annual William L. Benedict Memorial Lecture at its meeting Jan. 13, 1989. Charles K. La Pinta, Space Sciences Division, NASA Johnson Space Center, was the guest speaker. Dr. Benedict was president of the Ophthalmic Publishing Company at the time of his death in 1969.

International Strabismological Association: Sixth Congress

The Sixth Congress of the International Strabismological Association will be held March 11–16, 1990, in Queensland, Australia. For further information, write Dr. W. E. Gillies, 82 Collins St., Melbourne 3000 Australia.

National Eye Institute: Tenth Annual Clinical Vision Research Course

The National Eye Institute will hold the Tenth Annual Clinical Vision Research Course, April 26–29, 1989, in Longboat Key, Florida. For further information, write Catherine M. Beinhauer, Conference Management Associates, Inc., 127 Brook Hollow, Hanover, NH 03755.

Ninth International Congress of Eye Research

The Ninth International Congress of Eye Research will be held July 29 to Aug. 4, 1990, in Helsinki, Finland. For further information, write Ninth ICER Secretariat, Department of Anatomy, Eye Research Laboratory, University of Helsinki, Siltavuorenpenger 20 A SF-00170 Helsinki, Finland.

Satellite Symposium: Intraocular and Adnexal Tumors, and Orbital Diseases

A satellite symposium on Intraocular and Adnexal Tumors and Orbital Diseases will be held March 25–27, 1990, in Bali, as the satellite symposium of the International Congress of Ophthalmology, Singapore, March 18–24, 1990. For further information, write Secretariat, c/o P. T. Connexindo Pramadi Trimulya, P.O. Box 3400, Jakarta 10002 Indonesia.

Florida Society of Ophthalmology: Annual Meeting and Technicians Program

The Florida Society of Ophthalmology will hold its Annual Meeting and Technicians Program, March 17–19, 1989, in St. Petersburg, Florida. For further information, write Florida Society of Ophthalmology, 1133 W. Morse Blvd., Suite 201, Winter Park, FL 32789.

LSU Annual Conference: What's New and Important

The LSU Eye Center and LSU Medical Center will sponsor the LSU Annual Conference, What's New and Important, April 21 and 22, 1989, in New Orleans, Louisiana. For further information, write Adrienne Miester, LSU Eye Center, 2020 Gravier St., Suite B, New Orleans, LA 70112.

Mayo Clinic-Jacksonville: Ophthalmic Reviews

Ophthalmic Reviews 1989 will be given at the Mayo Clinic March 31 and April 1, 1989, in Jacksonville, Florida. For further information, write Marian Hunter, Mayo Clinic Jacksonville, 4500 San Pablo Rd., Jacksonville, FL 32224.

Memphis Eye Convention

The Memphis Eye Convention will be held March 11 and 12, 1989, in Memphis, Tennessee. For further information, write Thomas C. Gettelfinger, M.D., Director, Memphis Eye Convention, 6485 Poplar, Memphis, TN 38199.

Corneal Associates of New Jersey: First Annual Symposium

The Corneal Associates of New Jersey will hold its First Annual Symposium, April 1, 1989,

in Short Hill, New Jersey. For further information, write Theodore Perl, M.D., 101 Old Short Hills Road, West Orange, NJ 07052.

Ohio State University: Ninth Annual Ophthalmology Resident Alumni Research Symposium

The Ohio State University Department of Ophthalmology will hold its Ninth Annual Ophthalmology Resident Alumni Research Symposium, June 10, 1989. For further information, write Maureen A. Meck, Symposium Coordinator, Ohio State University Department of Ophthalmology, 456 W. 10th Ave., Columbus, OH 43210.

Pittsburgh Ophthalmological Society: Twenty-fifth Anniversary Spring Meeting

The Pittsburgh Ophthalmological Society will hold its Twenty-fifth Anniversary Spring Meeting, April 14 and 15, 1989, in Pittsburgh, Pennsylvania. For further information, write Pat Williamson, Executive Assistant, The Pittsburgh Ophthalmological Society, 2545 Mosside Blvd., Monroeville, PA 15146.

Stanford University Medical Center: Basic Science Course in Ophthalmology

Stanford University Medical Center Department of Ophthalmology will sponsor a Basic Science Course in Ophthalmology, July 4–Aug. 31, 1989, in Stanford, California. For further information, write J. W. Bettman, M.D., Department of Ophthalmology, A-157, Stanford Medical Center, Stanford, CA 94305.

Twentienth Jules Stein Lecture and Annual Postgraduate Seminar

The Twentieth Jules Stein Lecture and Annual Postgraduate Seminar will be held April 7 and 8, 1989, in Los Angeles, California. For further information, write Gretchen Falvo, Director of Academic Programs, OT-N22 Jules Stein Eye Institute, UCLA Medical Center, Los Angeles, CA 90024-1771.

Francis I. Proctor Foundation: Ophthalmology in the Third World: A Practical Orientation

The Francis I. Proctor Foundation will hold a meeting, Ophthalmology in the Third World: A Practical Orientation, March 8–10, 1989, in San Francisco, California. For further information, write Haas Foundation, c/o Proctor Medical Group, 95 Kirkham St., San Francisco, CA 94122.

National Eye Institute: Study of New Cyclosporine

The National Eye Institute is conducting a study of a new cyclosporine in the treatment of patients with endogenous, intermediate, and posterior uveitis who are considered corticosteroid or cytotoxic agent failures. Physicians with patients who may benefit should call (301) 496-3123 (Dr. Nussenblatt); or (301) 496-1243 (Dr. Alan Palestine or Ms. Susan Whitcher).

The National Eye Institute is also conducting a study of the antiviral agent Foscarnet in the treatment of cytomegalovirus retintis in AIDS patients. Physicians with patients who may benefit should call (301) 496-1243 (Dr. Judith Rubin).

Academia Ophthalmologica Internationalis: New Officers

At the annual meeting of the Academia Ophthalmologica Internationalis held in Sydney, Australia, Akira Nakajima of Tokyo was elected president to succeed Frederick C. Blodi of Iowa City. Giusseppe Scuderi of Rome and Helmut Fanta of Vienna were named vice presidents, succeeding Paul Bregeat and Edward Grom. Pierre Amarlic of Albi, France, succeeded Akira Nakajima as secretary-general. Werther Duque-Estrada of Rio de Janeiro continues as treasurer.

American Academy of Ophthalmology: 1989 Officers

Robert D. Reinecke has been named president of the American Academy of Ophthalmology. George E. Garcia is the new president-elect. The following have been elected to the Board of Directors: Claude L. Cowan, Jr., Oliver H. Dabezies, Edward K. Isbey, Jr., and Marilyn T. Miller, directors-at-large; B. Thomas Hutchinson, secretary for patient care and ophthalmic practice, and Dan B. Jones, secretary for instruction.

Personals

Denis Baylor

Denis Baylor of Stanford University School of Medicine received the 1988 Golden Brain Award from the Minerva Foundation.

Carl Kupfer

Carl Kupfer, Director of the National Eye Institute and President of the International Agency for the Prevention of Blindness, will deliver the Second Mohammed Aziz Memorial Annual Lecture: Blindness of the Tropics, March 16, 1989, in Baltimore, Maryland. The lecture is held in conjunction with the biannual meeting of the Program Advisory Group of the World Health Organization Prevention of Blindness Program, which is being held at the Dana Center as part of the Centennial Celebration of the Johns Hopkins Hospital.

John W. Shore

John W. Shore has been appointed director of Ophthalmic Plastic and Reconstructive Surgery for the Department of Ophthalmology at the Massachusetts Eye and Ear Infirmary. Previously Dr. Shore served as chairman of the Department of Ophthalmology and special assistant and consultant for ophthalmology to the United States Air Force Surgeon General at Wilford Hall United States Air Force Medical Center in San Antonio, Texas.

INSTRUCTIONS TO AUTHORS

For the preparation of typescripts for THE AMERICAN JOURNAL OF OPHTHALMOLOGY

THE AMERICAN JOURNAL OF OPHTHALMOLOGY publishes original articles, letters, editorials, abstracts, book reviews, and news items. Editorials, book reviews, and abstracts are published by invitation. Timely articles and letters dealing with original observations in clinical and basic ophthalmology are welcome. Each submission is evaluated by two or more scientific referees who recommend that the paper be (1) accepted as submitted, (2) returned for revision, or (3) rejected. Acceptance is determined by such factors as the originality, significance, and validity of the contribution, the suitability of the subject matter for subscribers to THE JOURNAL, and the editorial care with which the manuscript has been prepared.

One author should be designated as the corresponding author. This individual will be responsible for all questions concerning the preparation of the manuscript for publication. Authors are advised promptly of receipt of their papers. Within 45 days thereafter they are advised of acceptance, rejection, or the need for revision.

Disclosure and Copyright Transfer

At the time of submission, a signed copy of the disclosure and copyright transfer published in THE JOURNAL each month must be included with the manuscript. No article or letter will be reviewed until this disclosure and copyright transfer, signed by each author in the order that each name appears on the title page, has been received. The transfer must also list the home address of each author and the telephone number of the submitting author.

The manuscript must be original and may not contain data published previously or submitted for publication elsewhere. If data were presented at a scientific meeting, the place, date, and auspices of the meeting should be stated on the title page.

Mechanical Preparation of the Typescript

Submit an original and at least one duplicate copy of both the typescript and the illustrations. Xerographic copies are preferred to carbon copies.

Use 8 1/2 × 11-inch heavy, white, bond paper.

Provide 1 1/2-inch margins on all four sides of each page and indent paragraphs one-half inch.

The entire typescript, including title page, quotations, footnotes, acknowledgment, references, legends, and tables, must be double-spaced.

Use black, clearly legible type.

Use block type.

Do not underline.

Do not use italics or boldface.

Do not use all capitals.

Do not justify right margins.

Do not use a dot matrix printer. The type must be letter quality with clear, unbroken characters that do not touch or overlap.

Do not use any single-spacing.

Do not use condensed type.

Number each page in the upper right-hand corner. List the first author's name and short title (maximum, 60 characters and spaces) in the upper right-hand corner.

Spell out all terms except standard measurements, such as mm Hg, cm, and ml, used with numeric quantities; R.E. and L.E. may be used. Do not abbreviate IOP, CME, RPE, and the like, or use acronyms (BARD, ARN, ROP).

If percentages are used, the numerical equivalents must be included, for example, Of 80 patients, 20 (25%) had retinitis pigmentosa.

Prepare references, legends, and tables in THE JOURNAL form. (See following detailed instructions.)

Original Articles

The manuscript should be arranged in the following order: (1) Title page; (2) Summary; (3) Introductory text; (4) Material and Methods or Case Reports; (5) Results; (6) Discussion; (7) References; (8) Legends for illustrations; (9) Tables.

Title page—The title page is page 1. It should contain the title, a brief heading (no more than

60 characters and spaces) in the upper right hand corner, and each author's name with the highest (one only) academic degree. The department and the institution where the study was performed should be indicated. Sponsoring organizations and grants are acknowledged on the title page.

Referring physicians, consultants, editorial assistants, photographers, artists, laboratory assistants, secretaries, and others who assist in preparation of a paper cannot be acknowledged however valuable their services.

The name and mailing address of the author to whom requests for reprints should be directed must be indicated.

Each page that follows the title page must be numbered consecutively, and must include the first author's name and the brief title in the upper right-hand corner.

Summary—Each article must have a summary that synthesizes specifically the content of the paper in no more than 150 words. It should include the main clinical or research data and findings but exclude speculation. The summary must be written so that the message of the full paper can be understood independently. It must not contain references, illustrations, tables, or data not included in the full text. It should not repeat or paraphrase the title. The summary should answer the questions: who or what was studied, why the study was done, the results, and the significance of the study.

Narration—Articles should be organized and prepared in the style used by THE JOURNAL. A brief introductory statement of the problem should be presented. Material and methods or the patient selection should then be precisely and clearly described in enough detail for a reader to replicate the study. Results of the study should be given, followed by a discussion. The discussion elucidates the results and must relate directly to the topic of the paper.

References—THE JOURNAL does not publish extensive bibliographic reviews. References must be numbered consecutively, both in the text and in the reference list. The author is responsible for complete and accurate references, including the proper capitalization and accent marks used in foreign-language publications.

Personal communications, posters, program abstracts, unpublished data, and oral discussions that the reader cannot retrieve should be kept to a minimum and must be incorporated into the text without reference numbers. References to studies that have been accepted but have not yet been published must indicate the publication in which they will be published. Primary, not secondary, sources must be cited. References to books must contain inclusive pages of the section cited. The names of all authors must be cited in the reference list. THE JOURNALdoes not use the term et al. The following style is used by THE JOURNAL for periodicals (1), for books (2), and for chapters in books (3).

1. Rinkoff, J., Machemer, R., Hida, T., and Chandler, D.: Temperature-dependent light damage to the retina. Am. J. Ophthalmol. 102:452, 1986.
2. Helveston, E. M.: Atlas of Strabismus Surgery, 3rd ed. St. Louis, C. V. Mosby, 1985, p. 156.
3. O'Connor, G. R.: Herpes zoster uveitis. In Kraus-Mackiw, E., and O'Connor, G. R. (eds.): Uveitis. Pathophysiology and Therapy. New York, Thieme-Stratton, 1983, pp. 56–65.

The originator of the personal communication must provide written permission to be quoted.

Abbreviations for periodicals are listed in Index Medicus: Am. J. Ophthalmol., Surv. Ophthalmol., Br. J. Ophthalmol., and the like. If there is any doubt about an abbreviation, the full name of the publication should be spelled out completely.

Illustrations—Graphs, diagrams, and photographs must not be mounted. Each illustration should be numbered and cited consecutively in the text. The illustration number, an arrow indicating the top of the picture, and the first author's name should be indicated on a label on the back.

The figure number, legend, or text should not appear on the face of an illustration.

Graphs, diagrams, and line drawings must be prepared by a professional artist on heavy white paper with India ink. Lighter lines should be used for axes than for data curves. Photographs must have a glossy finish and a sharp contrast. Lettering, arrows, and the like must be professionally applied. In a series of illustrations, all parts should be oriented in the same direction. Photographs should be the same size or slightly larger than the intended reproductions. Figure widths in The Journal are 3 inches (one column) and 6 ½ inches (two columns). Lettering must be planned with reductions to these sizes in mind; letters should be of uniform size and large enough to be read easily after reduction.

Cropping should be done to exclude nonpertinent material from photographs. The front

surface of each photograph should be marked with a grease pencil to show the area to be reproduced.

THE JOURNAL does not use stereoscopic illustrations.

Each illustration must have a descriptive legend. Legends should be typed consecutively on a page (separate from the illustrations themselves). Legends should be typed in the form used by the THE JOURNAL, as follows:

Fig. 1 (Jones, Smith, and Brown). Histologic section of the eye (hematoxylin and eosin, ×70).

If there are more than three authors, use Jones and associates.

If identifiable photographs of patients are submitted the author must supply THE JOURNAL with proof of informed consent.

Individual illustrations and legends are preferred to composites made up of two or more separate parts. If multiple-part illustrations are submitted, they should be labeled from left to right and from top to bottom as follows:

Fig. 1 (Jones, Smith, and Brown). Case 3. Top left, The patient preoperatively. Top right, Three days after surgery. Bottom left, Four months after surgery. Bottom right, One year after surgery.

Do not label composite illustrations with letters (for example, part A, part B, . . .). Composite figures must be planned with the dimensions of a JOURNAL page and the need for a legend considered.

The visual field charts used in THE JOURNAL will be supplied to authors on request without charge. Write to Editorial Administrative Assistant, American Journal of Ophthalmology, Tribune Tower, Suite 1415, 435 N. Michigan Ave., Chicago, IL 60611.

Color—Authors must contribute to the cost of color reproductions. The charge to authors for color is $500 per page of color. Both color transparencies and high-quality color prints must be submitted with the paper, together with a layout indicating the proposed distribution of the illustrations and legends.

Tables—Each table must have a title, be numbered with an arabic numeral, and be cited consecutively in the text.

Each table must be double-spaced and nothing in the table should be underlined. Photographically reproduced or reduced tables are not acceptable.

The first line of a table should have the table number. The second line should have the title of the table.

Vertical lines should not be used anywhere in the table.

All columns should be labelled; lengthy descriptions belong in the text or as a footnote to the table, not in the table itself. Tables should be used only for summarizing numeric data.

Abbreviations should be avoided. If necessary, they must be fully explained in a footnote. The following symbols are used for footnotes in the order indicated: * (asterisk), † (dagger), ‡ (double dagger), § (section mark), ‖ (parallels), ¶ (paragraph mark), and # (number sign).

Proofs—A copy of the edited typescript is sent to the corresponding author. Author corrections must be entered in red ink. Each author query must be answered. Corrections are minimized by careful initial preparation of the manuscript.

The typescript must be returned to the Manuscript Editor, Ophthalmic Publishing Company, Suite 1415, 435 N. Michigan Ave., Chicago, IL 60611, within 48 hours of receipt. Failure to return the typescript promptly delays publication.

Reprints—Reprints must be ordered promptly. A reprint order form is sent to the submitting author four to six weeks before publication of the article.

Letters to THE JOURNAL

Letters describe unusual clinical or pathologic findings, experimental results, and new instruments and techniques. Letter typescripts should be prepared in the same way as Original Articles. They must be no more than five pages in length (title page, two pages of text, reference page, and legend page). References must be limited to five. No more than two black-and-white illustrations, 3 inches wide (one column in width), may be used. Color illustrations cannot be used.

The Editorial Board either accepts or rejects letters. They are not returned with suggestions for revision. Since these instructions markedly limit the opportunity for an extended discussion or review, THE JOURNAL does not publish correspondence concerning letters.

Correspondence

Correspondence concerning recent articles or other material published in THE JOURNAL should be submitted within six weeks of publication. Correspondence typescripts should be prepared in the same way as an Original Article

and should be no more than two typewritten pages in length. Every effort will be made to resolve controversies between the correspondents and the authors of the article before formal publication.

News Items

THE JOURNAL welcomes information concerning meetings, honors, and appointments. Only one new item should be included on each page. News items should be double-spaced and provide the name and address of the responsible author.

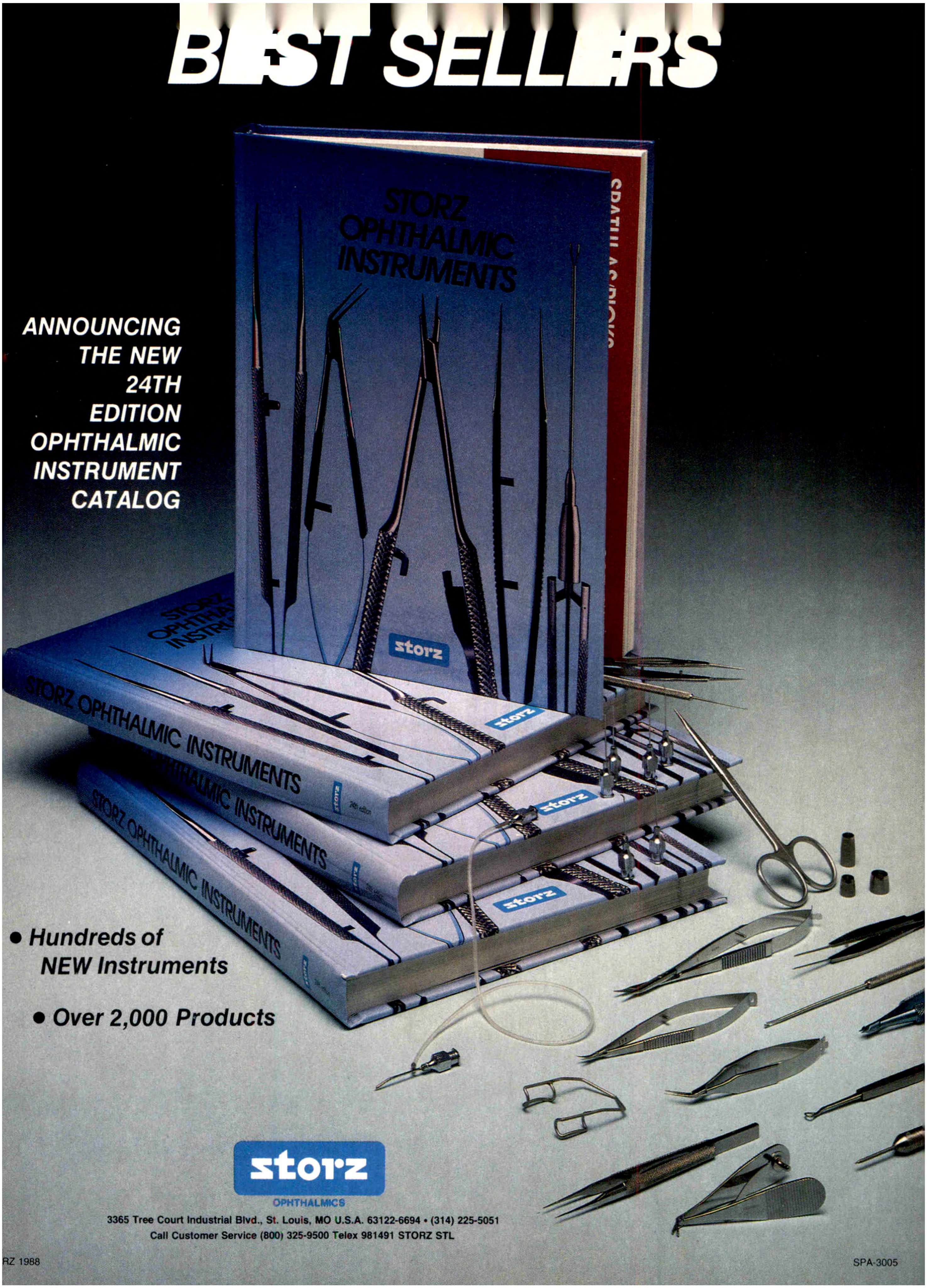
Source Texts

THE JOURNAL recommends the following publications as guides to style, grammar, and spelling:

CBE Style Manual Committee: Council of Biology Editors Style Manual. A Guide for Authors, Editors and Publishers in the Biological Sciences, 5th ed. Bethesda, Council of Biology Editors, 1983.

The Chicago Manual of Style, 13th ed. Chicago, University of Chicago Press, 1982.

Strunk, W., Jr., and White, E. B.: The Elements of Style, 3rd ed. New York, Macmillan Publishing Co., 1979.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NEW PRODUCTS AND SERVICES

New products and services considered by the editors to be of interest to our readers are described on the basis of information supplied by the companies cited. Publication of these notices does not imply endorsement or warranty by The Ophthalmic Publishing Company, publishers of The American Journal of Ophthalmology, for these products and services.

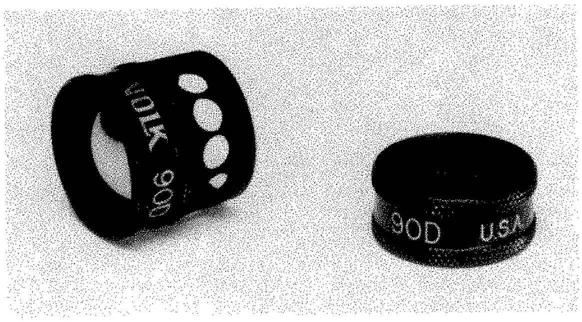
Pharmaceuticals

Dakryon
301 Utica Ave.
Lubbock, TX 79416
Tel: (806) 797-7674

Dakryon announced the introduction of two artificial tear products developed by Frank J. Holly, Ph.D. Dwelle contains a synergistic polymer mixture to ensure complete wetting and has high colloid osmolality to promote healing and adherence of corneal epithelium damaged by dry eye conditions. Dakrina contains vitamin A solubilized by a polymer carrier and vitamin C to assist healing of squamous metaplasia of ocular surface epithelium in dry eye patients. Both eyedrops are available in 15-ml bottles.

Diagnostic Lenses

Volk Optical
7893 Enterprise Dr.
Mentor, OH 44060
Tel: (216) 942-6161

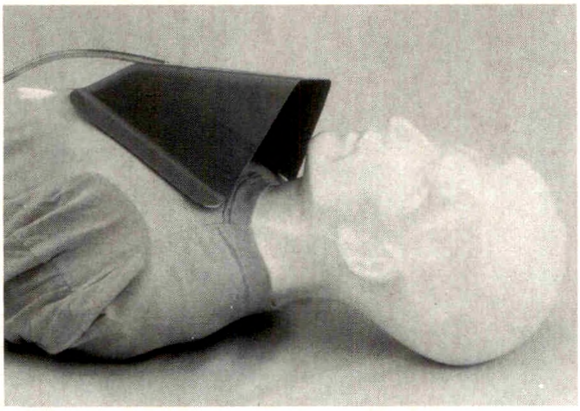


Volk Optical has developed a Lid Lens Adapter for the Volk 90-D lens. The adapter fits into both the original 20-mm and the new 21.5-mm Volk 90-D lenses, providing immediate aerial image observation as well as exact lens positioning, lens stability, and eyelid control, without contacting the cornea. No anesthetic is needed. The Lid Lens Adapter unit comfortably rests on the eyelids. The convenient friction fit provides for easy insertion and removal for 90-D use with or without the Lid Lens Adapter. Price: $33.

The new 21.5-mm Volk 90-D lens diameter provides a sweeping 63-degree field of view, and the retaining ring diameter provides motility and ease of handling. The single-element Volk 90-D yellow lens avoids third and fourth surface reflections and ghost images inherent in add-on filter systems. The Volk Double Aspheric optical design eliminates field curvature and astigmatism for clearest fundus imaging. Additionally, the thin lens design minimizes chromatic aberration. Available in both clear and Volk yellow retinal protector glass, the 90-D lens features high efficiency and durable, broad-band, multilayer, antireflection coating.

Surgical Devices

Hi-Line Medical
22642 Lambert
Suite 407
El Toro, CA 92630
Tel: (800) 524-6007

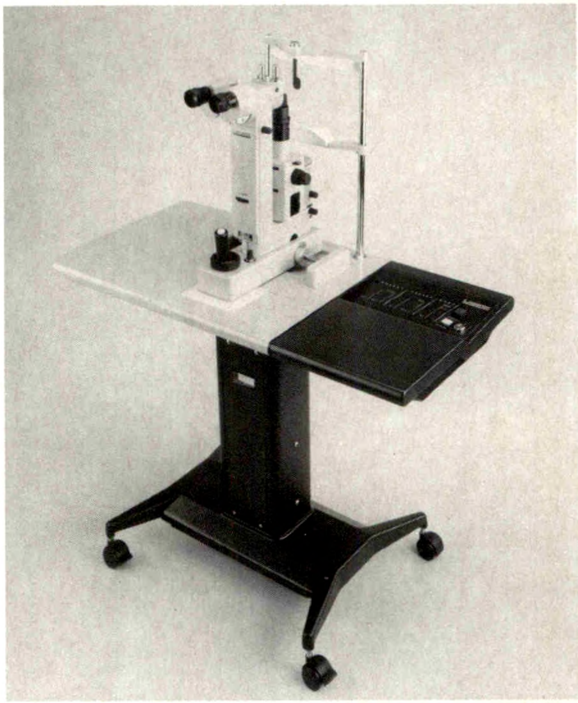


Ipax, Inc. and Hi-Line Medical, Inc. have introduced the reusable plastic SureBreath Dome, designed to elevate the surgical drape and increase patient comfort during ophthalmic surgery. Because the SureBreath Dome rests on the chest, the patient's face is free of taped paper arches and oxygen lines. The patient breathes from a reservoir of oxygen created underneath the dome with no sense of suffocation. The dome is designed with a low, horizontal profile so that the instrument mayo stand can be positioned directly over the patient's chest. Set up is easy and the oxygen line is held securely within the groove of the dome. The plastic SureBreath Dome can be reused by simply transferring the device between patients once the setup is complete.

Lasers

Keeler Instruments, Inc.
456 Parkway
Broomall, PA 19008
Tel: (800) 523-5620 (National)
(215) 353-4350 (Pennsylvania)

A new generation YAG laser, Keeler Laserex system is contained within the slit-lamp arm so no hoses, wires, or boxes infringe upon the operating space. There is nothing between the surgeon and the patient except the slit lamp.



With low energy, using less than 0.4 mJ, the Keeler Laserex performs posterior capsulotomies. The Laserex is designed for minimal service and maximum reliable performance. The design uses only one mirror, and a special steel track within the slit-lamp arm ensures correct alignment even when the modular components are exchanged.

Contact Lenses

Allergan Optical
2525 DuPont Dr.
Irvine, CA 92715
Tel: (714) 752-4500

Allergan Optical introduced the Allergan Advent contact lens (developed and manufactured by 3M) in a regional launch in Southern California. Additional roll-outs will follow in the coming months.

The Allergan Advent lens marks the entry of a new category in the contact lens arena—Flexible Fluoro-Polymer. This lens material combines flexibility, wettability, deposit resistance, and a high degree of visual acuity with excellent oxygen permeability and transmissibility. It is approved by the Federal Food and Drug Administration for both daily and up to seven days overnight extended wear.

The future of ophthalmic lasers is taking shape.

Announcing VISULAS™ Argon, one of three new lasers that establish Carl Zeiss as the ophthalmic laser company of the future.

The VISULAS Argon system is the *only* complete coagulation laser with superb Zeiss optics, including the revolutionary Zeiss 30SL/L Slit Lamp, against which all others must now be measured.

The high-performance laser tube, compact control panel, and asymmetrical table are optimally designed for doctor/patient convenience and safety.

The experience and skill of Carl Zeiss in precision optics, mechanics, and engineering make VISULAS Argon and its companion products, VISULAS YAG and VISULAS Argon/YAG Combination, the best performing ophthalmic lasers available to U.S. ophthalmologists.

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Punctal Occlusion and Topical Medications for Glaucoma

Timothy C. Huang, M.D., and David A. Lee, M.D.

We studied the effects of punctal occlusion on the intraocular pressures of patients treated with topical medications for glaucoma. Silicone punctal plugs were used to occlude the inferior punctum of one eye in each of 19 patients treated with identical antiglaucoma eyedrops in both eyes. The intraocular pressures before and after punctal occlusion were compared. The eyes with the punctal plugs showed a statistically significant ($P < .0001$) decrease in pressure of 1.32 mm Hg after punctal occlusion when compared to that of the fellow control unplugged eyes. The intraocular pressures in the plugged eyes decreased an average of 1.82 mm Hg after punctal occlusion when compared to before punctal occlusion ($P = .001$). The intraocular pressure in the unplugged control eyes did not change significantly after punctal occlusion of the fellow treated eye.

© American Journal of Ophthalmology 107:151–155, February, 1989

Acute Closed-Angle Glaucoma After Arteriovenous Fistulas

Stuart Fourman, M.D.

Unilateral secondary acute closed-angle glaucoma was associated with a ciliochoroidal detachment in two patients. One patient, aged 17 years, had an orbital arteriovenous fistula. The other patient, aged 73 years, had a dural arteriovenous fistula that originated from branches of the right internal maxillary artery. In each patient there was increased intraocular pressure, a moderately shallow central anterior chamber, and a flat peripheral anterior chamber. The ciliochoroidal detachment was postulated to displace the iris-lens diaphragm, resulting in the closed angle. Closure of the orbital fistula in the 17-year-old patient reduced the ciliochoroidal detachment and relieved the glaucoma, but visual acuity was reduced to 20/200. The glaucoma in the 73-year-old patient was relieved with topical instillation of timolol 0.5%, homatropine 5%, and systemic administration of acetazolamide. The fistula closed spontaneously, with relief of other ocular signs of the arteriovenous fistula.

© American Journal of Ophthalmology 107:156–159, February, 1989

Immunohistologic Findings and Results of Treatment With Cyclosporine in Ligneous Conjunctivitis

Edward J. Holland, M.D., Chi-Chao Chan, M.D., Toichiro Kuwabara, M.D., Alan G. Palestine, M.D., J. James Rowsey, M.D., and Robert B. Nussenblatt, M.D.

Using immunohistochemical techniques, we studied ligneous conjunctival lesions from two patients. A significant immune reaction was detected that was characterized by activated T lymphocytes and focal accumulation of plasma cells and B lymphocytes. Immunofluorescent studies demonstrated that IgG was a prominent component of the amorphous hyaline material seen in these lesions.

After previous treatment methods had failed, both patients were treated with excisional biopsy and topical cyclosporine. Patient 1 had a dramatic response, with complete resolution of the lesions. Patient 2 had a significant improvement resulting in small, slow-growing recurrences instead of the rapid and extensive recurrences that occurred before treatment with cyclosporine.

© American Journal of Ophthalmology 107:160–166, February, 1989

Acute Hydrops in Pellucid Marginal Corneal Degeneration

John B. Carter, M.D., Dan B. Jones, M.D., and Kirk R. Wilhelmus, M.D.

Three patients had pellucid marginal corneal degeneration complicated by corneal edema. The corneal edema appeared to be a result of a break or detachment of Descemet's membrane as a result of increasing corneal ectasia. The disruption in Descemet's membrane began just above the inferior, crescent-shaped area of stromal thinning. Therapeutic modalities initially included hypertonic solution to determine whether corneal edema would resolve spontaneously, apparently by endothelial migration with healing over the break in Descemet's membrane. One patient required thermokeratoplasty and another penetrating keratoplasty for persistent stromal edema. Acute hydrops can occur with pellucid marginal corneal degeneration by a pathogenesis similar to other noninflammatory corneal thinning disorders such as keratoconus.

© American Journal of Ophthalmology 107:167–170, February, 1989

Ultrastructural Studies of Vitreomacular Traction Syndrome

William E. Smiddy, M.D., W. Richard Green, M.D., Ronald G. Michels, M.D., and Zenaida de la Cruz, B.S.

We performed electron microscopic studies on seven specimens removed from the posterior retina at the time of vitrectomy for vitreomacular traction syndrome. Fibrous astrocytes were the predominant cell type in all cases. Fibrocytes were present in two cases and myofibrocytes were seen in three cases. Additional cellular and extracellular features included fragments of internal limiting membrane in six cases, old collagen in all cases, new collagen in one case, occasional macrophages in four cases, and fibrous astrocytes with myofibroblastic differentiation in one case.

© American Journal of Ophthalmology 107:177–185, February, 1989

The Management of Retinal Detachment Complicating Degenerative Retinoschisis

John S. Ambler, F.R.A.C.O., Sanford M. Meyers, M.D., Hernando Zegarra, M.D., and Froncie A. Gutman, M.D.

We repaired six retinal detachments complicating degenerative retinoschisis by using simultaneous external subretinal fluid drainage and intraocular gas injection without a scleral buckle or vitrectomy. The outer wall breaks were 30 to 135 degrees in size, and in three cases, extended close to the arcade vessels. We achieved retinal reattachment and collapse of the schisis cavity at surgery in all six cases. In one case, the retina redetached postoperatively, but it was repaired with a scleral buckle and gas injection. This technique simplified the management of retinal detachments complicating degenerative retinoschisis, particularly those with large or posterior outer-layer breaks.

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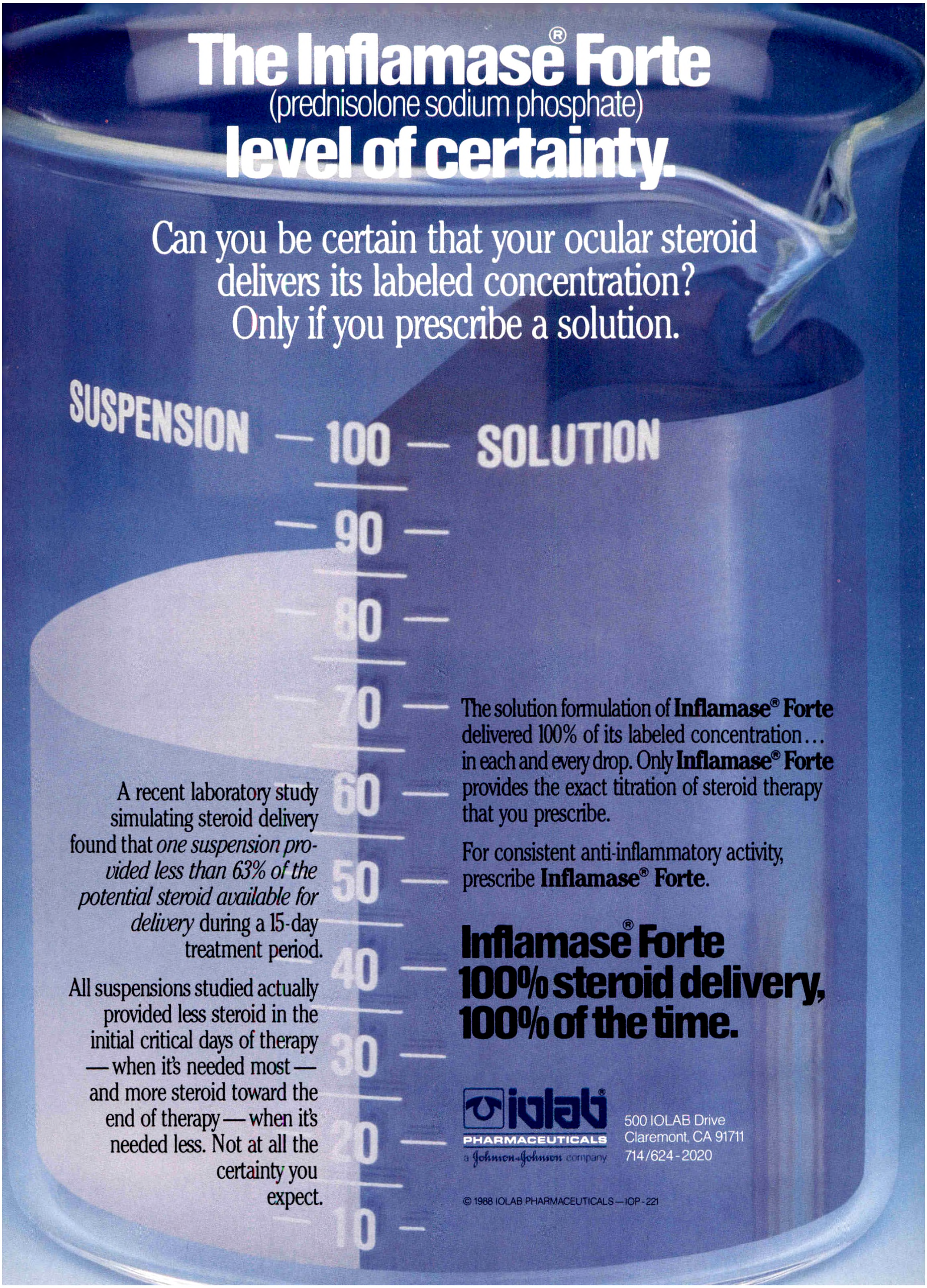
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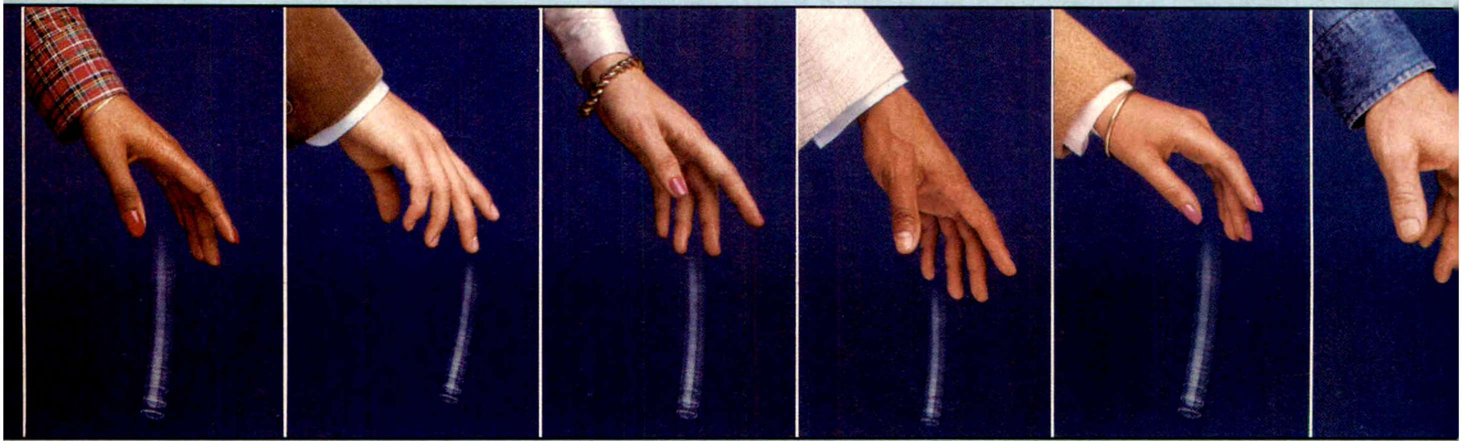

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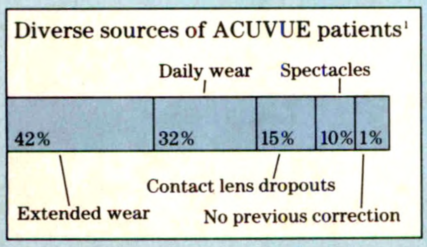

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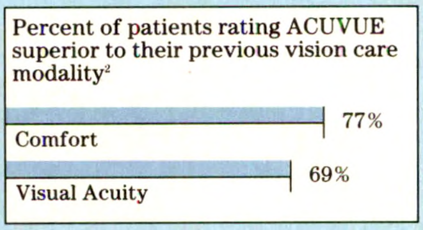

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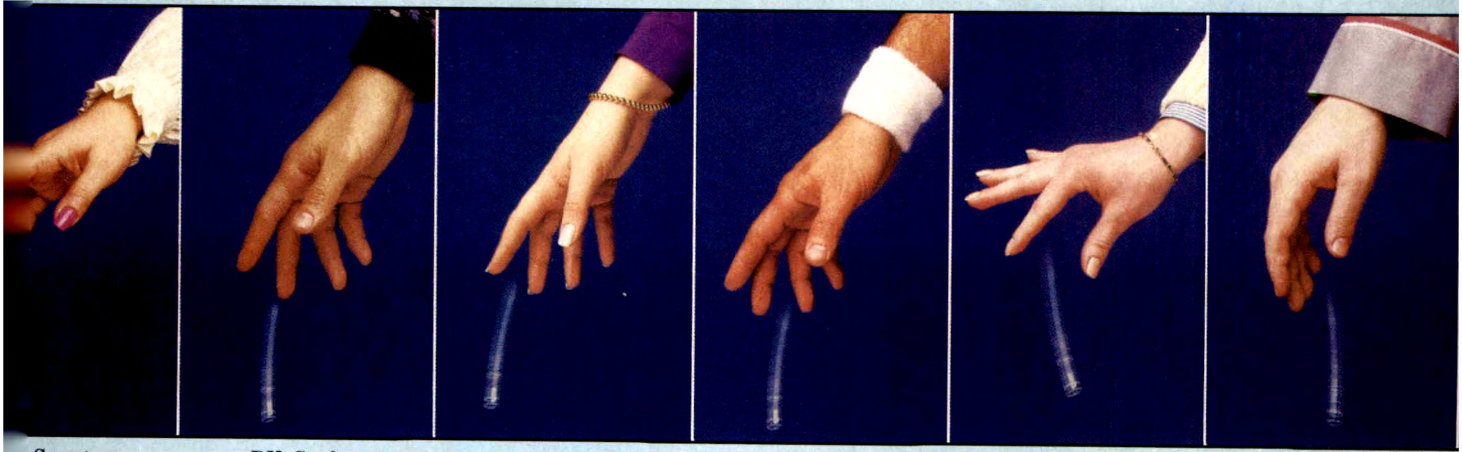

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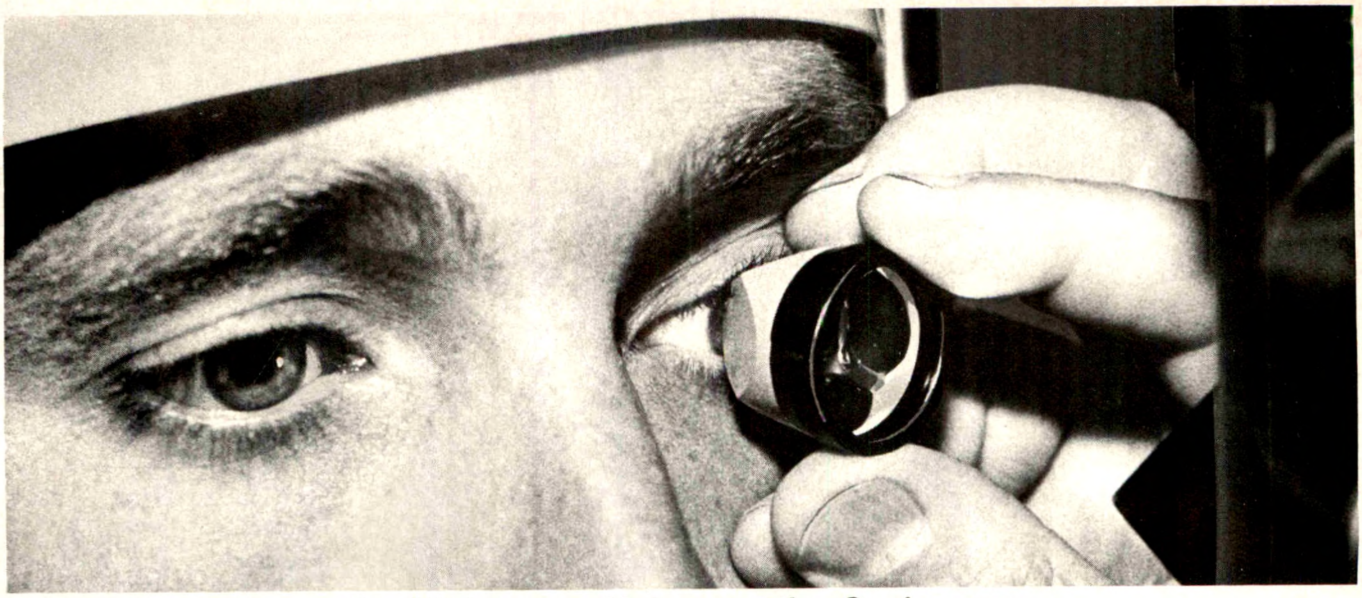

Corneal Topography of Early Keratoconus

Leo J. Maguire, M.D., and William M. Bourne, M.D.

We used a corneal topography analysis system to evaluate nine eyes of seven patients in whom the diagnosis of keratoconus was suspected. There was no slit-lamp evidence of the condition. In seven of nine eyes a cone was identified. Large amounts of corneal distortion were seen in selected patients even though they had excellent spectacle-corrected visual acuity and little or no distortion of the keratometer mires. These findings suggest that corneal topography analysis systems are useful in the detection and description of corneal irregularity in the early stages of keratoconus. The radial keratotomy surgeon should be aware that normal results on slit-lamp examination and normal keratometry and refractive data do not rule out the presence of early keratoconus.

Corneal Ulcers Associated With Disposable Hydrogel Contact Lenses

James P. Dunn, Jr., M.D., Bartly J. Mondino, M.D., Barry A. Weissman, O.D., Paul B. Donzis, M.D., and Don O. Kikkawa, M.D.

Four patients developed corneal ulcers associated with the use of disposable extended-wear hydrogel contact lenses. Bacteria were recovered from corneal ulcers in three of the patients. Three patients discarded their contact lenses after ten or more days of extended wear; the corneal ulcers in these patients developed toward the end of the wearing cycle. The fourth patient removed her contact lenses every two days for cleaning and disinfection and discarded them for a new pair on a weekly basis. Improper lens hygiene was noted in only one patient. All corneal ulcers responded to antibiotic treatment. In three patients visual acuity returned to normal, but scarring of one patient's cornea resulted in a visual acuity of 20/60.

Clinical Indications for and Procedures Associated With Penetrating Keratoplasty, 1983–1988

Steven E. Brady, M.D., Christopher J. Rapuano, M.D., Juan J. Arentsen, M.D., Elisabeth J. Cohen, M.D., and Peter R. Laibson, M.D.

We reviewed the preoperative clinical indications and associated surgical procedures for 2,299 penetrating keratoplasties performed at our institution from 1983 through 1988. Pseudophakic bullous keratopathy was the most common indication overall, accounting for 526 cases (23%). A marked increase was noted in the incidence of pseudophakic bullous keratopathy as an indication for penetrating keratoplasty beginning in 1985. The association of anterior chamber intraocular lenses in eyes with pseudophakic bullous keratopathy undergoing penetrating keratoplasty increased from 19 of 43 cases (44%) in 1983 to 79 of 108 cases (73%) in 1988. The incidence of intraocular lens exchange at the time of penetrating keratoplasty in cases of pseudophakic bullous keratopathy increased from six of 43 (14%) in 1983 to 63 of 108 (58%) in 1988.

Other major indications for penetrating keratoplasty included Fuchs' dystrophy (375 cases, 16%), keratoconus (348 cases, 15%), aphakic bullous keratopathy (331 cases, 14%), and regraft (233 cases, 10%). Cataract extraction, with or without intraocular lens implantation, was combined with penetrating keratoplasty in 397 of 1,532 phakic eyes (26%). The incidence of triple procedure (penetrating keratoplasty, cataract extraction, and intraocular lens implantation) increased from 27 of 248 phakic eyes (11%) in 1983 to 68 of 258 phakic eyes (26%) in 1988.

Familial Congenital Cornea Guttata With Anterior Polar Cataracts

Elias I. Traboulsi, M.D., and Richard J. Weinberg, M.D.

We examined 21 members of a family with a syndrome of cornea guttata and anterior polar cataracts. Twelve members had both ocular abnormalities. An affected woman underwent penetrating keratoplasty at age 28 years. Light microscopy of the corneal button showed changes consistent with cornea guttata and corneal edema. The combination of cornea guttata and anterior polar cataracts appears to form a well-defined ocular syndrome that is inherited in an autosomal dominant fashion.

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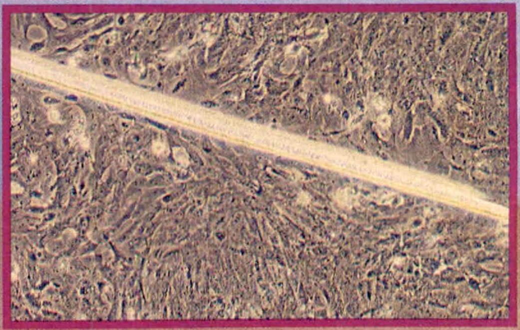

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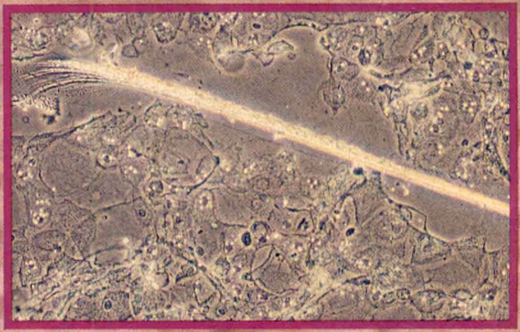

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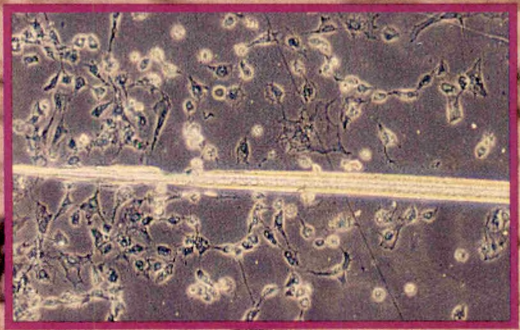

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2. Tripathi: Which ophthalmic and lens care preservatives are safe? Abstract for International Congress of Ophthalmology, Rome, May 1986.
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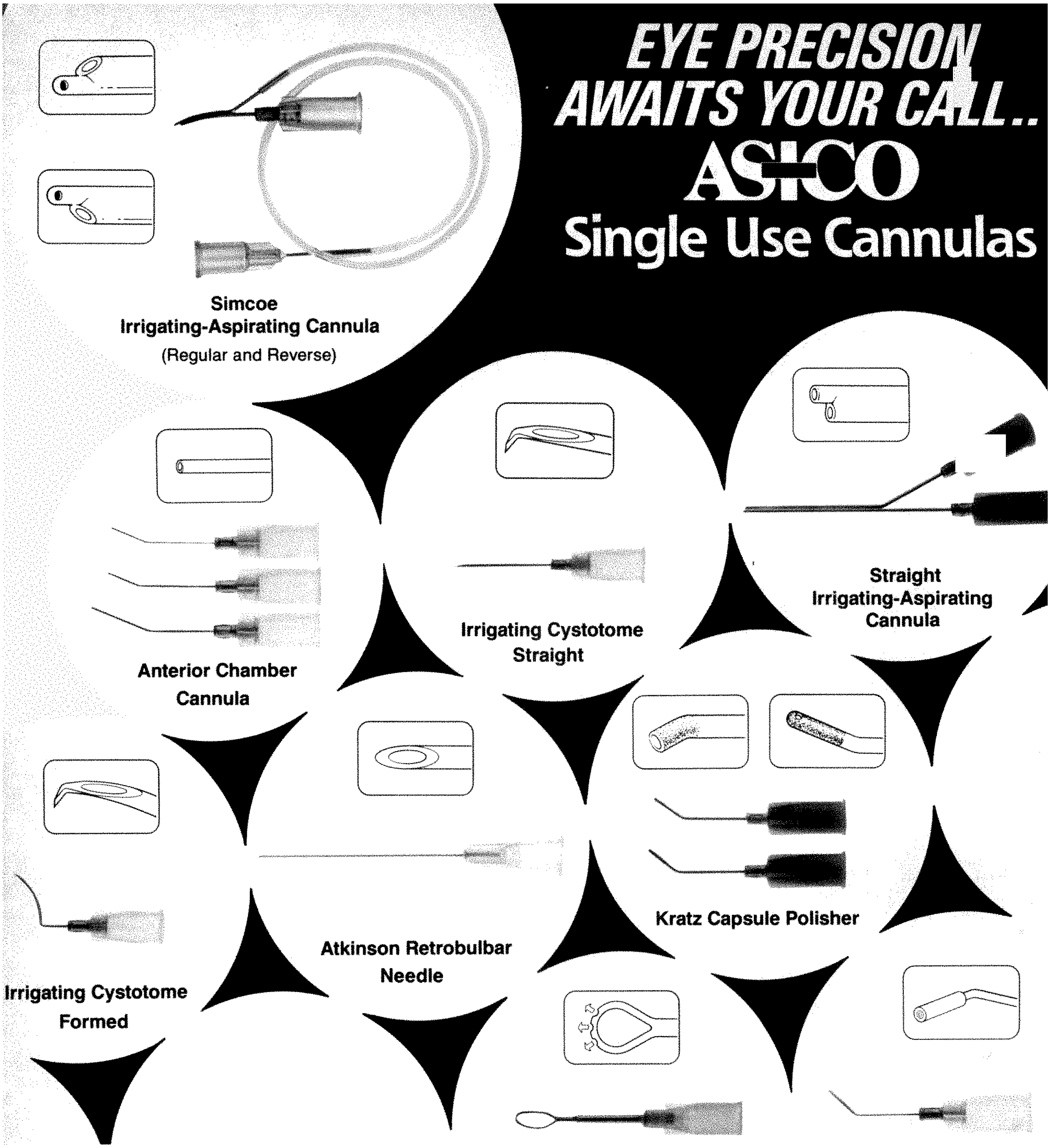

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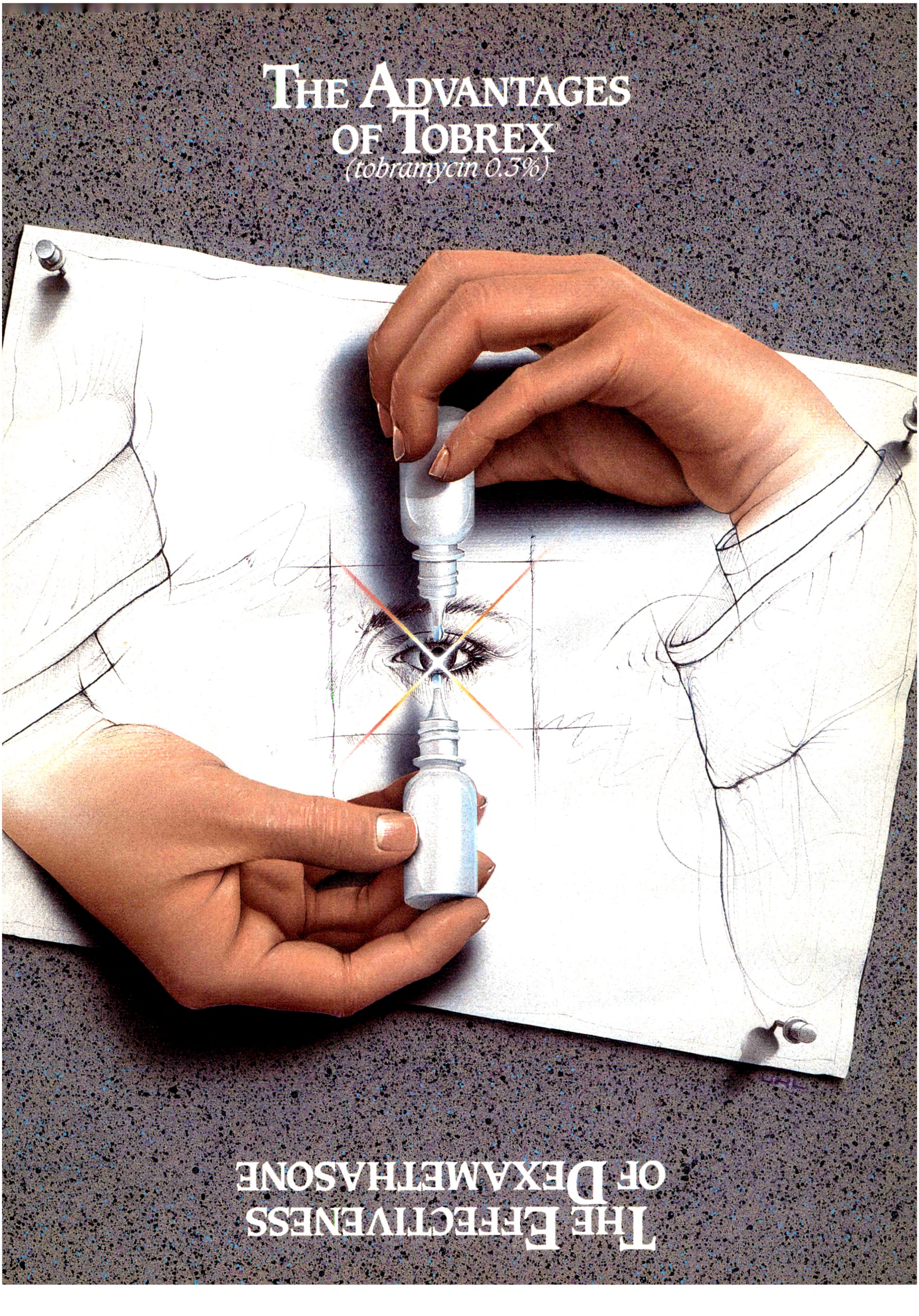
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The Effect of Increased Intraocular Pressure on Visual Acuity and Corneal Curvature After Radial Keratotomy

Sandy T. Feldman, M.D., Joseph Frucht-Pery, M.D., Robert N. Weinreb, M.D., Arturo Chayet, M.D., Andreas W. Dreher, Ph.D., and Stuart I. Brown, M.D.

To detect the effect of increased intraocular pressure on visual acuity and corneal curvature after radial keratotomy, we measured these variables in the sitting and inverted positions in 18 patients who underwent radial keratotomy (Group 1) and compared their results with those from the unoperated on eyes of seven patients (Group 2). We also compared the results before and after inversion within each group. Intraocular pressure increased to approximately two times normal in each group. Significant improvement in visual acuity and reduction in central keratometry were noted only in Group 1. By multiple regression analysis, visual improvement correlated with the number of incisions but not the time since surgery. Our study provides evidence that increased intraocular pressure may account for transient changes in vision and corneal curvature after radial keratotomy.

© American Journal of Ophthalmology 108:126–129, August, 1989

Test-Retest Variability in Glaucomatous Visual Fields

Anders Heijl, M.D., Anna Lindgren, M.S., and Georg Lindgren, Ph.D.

We measured test-retest variations in computerized visual fields from glaucomatous eyes. Fifty-one patients were tested four times within a four-week period; the severity of disease varied from incipient to advanced. We determined the dependence of threshold variability on defect depth and test point location. In areas of the visual field initially found to have moderate loss of sensitivity, variation in follow-up measurements ranged from normal sensitivity to absolute defect, with little dependence on distance from fixation. Conversely, large changes were considerably more unusual in locations initially showing normal or near-normal sensitivities, and variability was lowest in the most central portion of the field. Our findings suggest that differentiation between true progression and random variation will be facilitated if these factors are taken into account, as well as if comparisons are based on more than two tests. The complex nature of intertest variation in glaucoma makes it natural to approach this problem with the help of computer-assisted analyses.

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Complications After Surgery for Congenital and Infantile Cataracts

Ronald V. Keech, M.D., Andrea Cibis Tongue, M.D., and William E. Scott, M.D.

We reviewed the records of 78 patients who underwent 128 surgical procedures for congenital or infantile cataracts before age 30 months for the type and frequency of postoperative complications. The surgeries included 92 limbal lensectomies and anterior vitrectomies, 13 pars plicata lensectomies, 20 aspirations, and three additional procedures. Complications developed after 21 of the 105 lensectomy and anterior vitrectomy procedures. Ten eyes (10%) required additional surgery for a secondary membrane, 12 eyes (11%) developed glaucoma, and one (1%) developed a retinal detachment. Patients who underwent surgery by 8 weeks of age had a significantly greater number of complications ($P < .025$). Patients undergoing cataract surgery early in life should be routinely examined for possible postoperative glaucoma. The best method for reducing secondary membrane formation and some types of glaucoma appears to be an extensive removal of the lens cortex, posterior capsule, and anterior vitreous.

© American Journal of Ophthalmology 108:136–141, August, 1989

Ocular Surgery on Patients Receiving Long-Term Warfarin Therapy

Steven P. Gainey, M.D., Dennis M. Robertson, M.D., William Fay, M.D., and Duane Ilstrup, M.S.

We analyzed data of 50 patients receiving long-term warfarin sodium therapy who underwent ocular surgery between 1982 and 1986. The frequency of hemorrhagic and thrombotic complications was compared in patients in whom anticoagulants were continued, those in whom the anticoagulants were discontinued in the perioperative period, and a group of matched control patients. There were six perioperative hemorrhagic complications in the warfarin-treated group (12%) compared to none in the control group. This difference was significant ($P < .03$). However, no significant difference in hemorrhagic complications was seen between patients in whom warfarin sodium was continued and those in whom it was discontinued.

© American Journal of Ophthalmology 108:142–146, August, 1989

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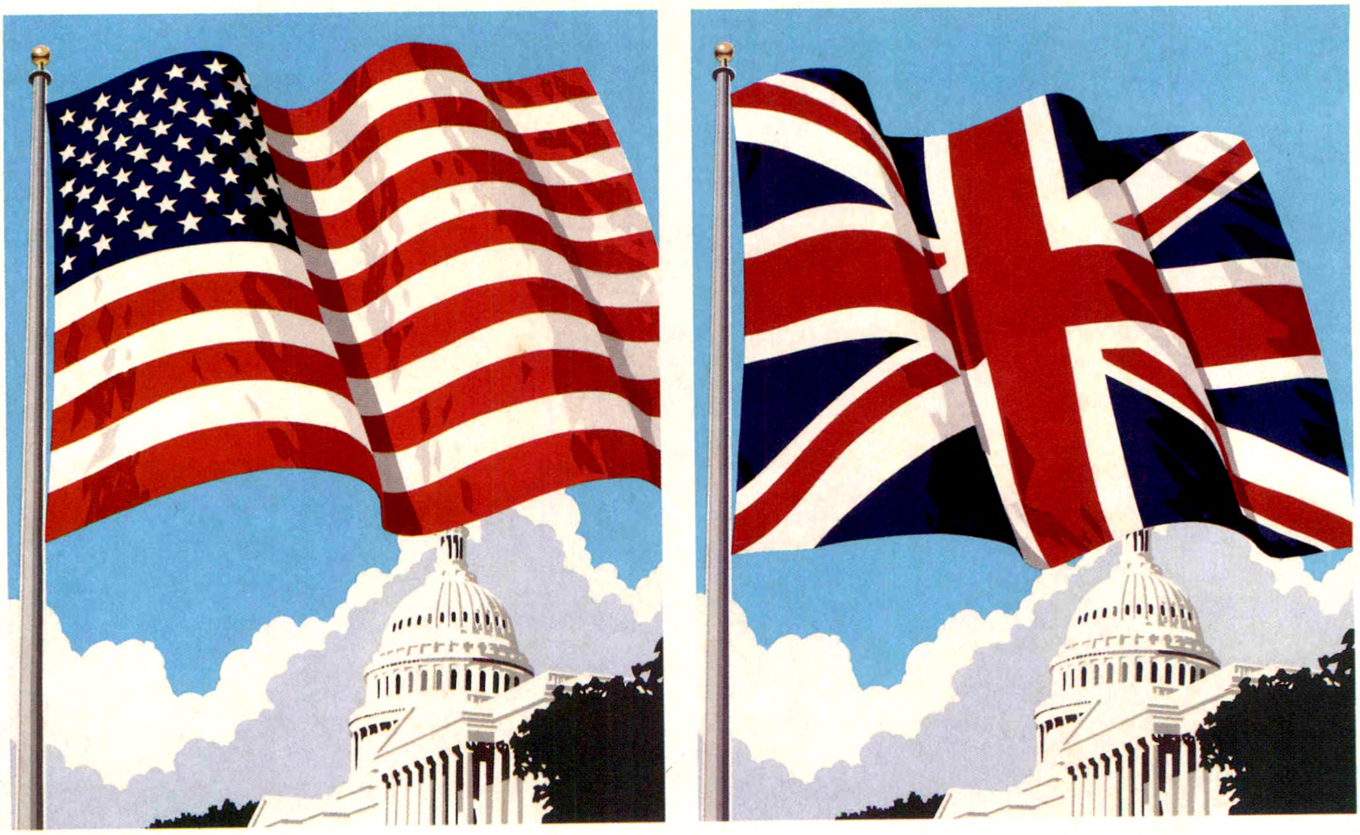

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VOLUME 108 NUMBER 2 AUGUST, 1989

Corneal Topography of Early Keratoconus

Leo J. Maguire, M.D., and William M. Bourne, M.D.

We used a corneal topography analysis system to evaluate nine eyes of seven patients in whom the diagnosis of keratoconus was suspected. There was no slit-lamp evidence of the condition. In seven of nine eyes a cone was identified. Large amounts of corneal distortion were seen in selected patients even though they had excellent spectacle-corrected visual acuity and little or no distortion of the keratometer mires. These findings suggest that corneal topography analysis systems are useful in the detection and description of corneal irregularity in the early stages of keratoconus. The radial keratotomy surgeon should be aware that normal results on slit-lamp examination and normal keratometry and refractive data do not rule out the presence of early keratoconus.

Keratoconus is a noninflammatory corneal thinning disorder characterized in its most advanced form by a localized conical protrusion of the cornea associated with an area of corneal stromal thinning most marked at the apex of the cone.[1,2] When the characteristic slit-lamp findings of advanced keratoconus are seen, the diagnosis can be made readily. The earliest stages of keratoconus usually develop between puberty and 30 years of age.[3] The astute clinician suspects the condition in adolescents and young adults who complain of progressive myopic astigmatism and subtle spectacle blur even when classic slit-lamp findings are not present. The finding of a focal round or oval area of internal reflection in the central or inferior cornea while inspecting the red reflex with the direct ophthalmoscope helps confirm the diagnosis.[1,2]

As early as 1946 Amsler[4] recognized the utility of photokeratoscopy in the detection of the early stages of keratoconus in which spectacle-corrected visual acuity may still be excellent and slit-lamp findings of the condition minimal to nonexistent. Rowsey, Reynolds, and Brown[5] described similar findings. Recent advances in computer-based analysis of keratoscope images[6-8] now offer the opportunity to evaluate in exquisite detail the patterns of power distribution seen in the earliest stages of keratoconus and offer the opportunity for earlier diagnosis and a better understanding of the degree of corneal irregularity compatible with a given level of visual function. We used a highly sensitive computer-based corneal topography analysis system to try to detect the presence of keratoconus in patients without slit-lamp evidence of the disease who had normal keratometry readings and excellent spectacle-corrected Snellen visual acuity.

Material and Methods

From May 1988 through January 1989, we performed topographic analysis on a group of eyes in which no slit-lamp evidence of keratoconus (stromal thinning, Fleischer's ring, Vogt's striae, anterior stromal scar) was found but in whom the diagnosis was suspected. Of the seven patients in the study, five had defi-

Accepted for publication May 2, 1989.
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nite slit-lamp evidence of keratoconus in the fellow eye. In the remaining two patients no slit-lamp evidence of keratoconus was found in either eye, but the diagnosis was entertained because of patient complaints of mild spectacle blur in at least one eye despite best-corrected visual acuity of 20/30 or better. None of the eyes with suspected keratoconus showed slit-lamp evidence of the condition. In all cases best-corrected visual acuity with spectacles was 20/30 or better, with less than 2.25 diopters of cylinder in the spectacle refraction. No patient had more than 3 diopters of keratometric astigmatism (Table). Patients 1 and 7 had worn a soft contact lens in the eye studied.

We obtained keratoscope images of the study eyes with the Corneal Modeling System (Computed Anatomy, New York, New York), a computer-based corneal topography analysis system.[8] Four keratoscope video images were captured for each eye. The technician did not accept to computer memory any image for which the aiming laser images were not exactly superimposed, any image in which patient fixation was in doubt, or any image showing evidence of tear film artifact.

All video images were processed using the revised Corneal Modeling System analysis software updated in May 1988. Notation was made of any errors in the autodigitizing process. The video images were ranked in order of overall quality, taking into consideration the amount of surface area covered by the keratoscope mires and the quality of the autodigitizing process. The image with the highest rank was used later to generate the color-coded topography maps. None of the maps were generated until after collection of all visual acuity data. In those cases in which a cone was identified on the topography maps, we determined corneal power at the cone apex and the location of the apex of the cone relative to the visual axis point.

Results

Of the nine eyes studied, seven showed definite evidence of early keratoconus. The cone apex was located 1.3 to 2.5 mm from the visual axis in all patients. All cones were located inferior to the visual axis between the 245- and the 301-degree hemimeridians. The degree of irregularity observed varied widely between patients.

The most subtle cone detected was in the left eye of Patient 7 (Fig. 1). In this case each color in the contour map represents a small (0.3-diopter) range in surface power. Colors in the blue spectrum represent lower powers and colors closer to the red spectrum represent higher powers. Power in this case ranges from a low of 41.5 to greater than 44.5 diopters. The area of the cone apex, identified by the red color interval, is surrounded by concentric bands of increasingly lower corneal power. Lowest corneal power is seen in the superior half of the cornea.

The most advanced cones observed were in the left eye of Patient 2 (Fig. 2) and the left eye of Patient 3 (Fig. 3). In Figure 2, each color represents a 1.1-diopter range of power and overall power ranges from 39.9 to greater than 50.9 diopters. In Figure 3, each color represents a 1.2-diopter range and the overall range is between 38.9 and greater than 50.9 diopters. Both of these patients had excellent spectacle-corrected visual acuity and less than 2 diopters of keratometric astigmatism despite the presence of this degree of irregularity (Table).

The power distribution in the other patients with identifiable cones showed similar patterns to those shown in Figures 1 through 3, with degrees of irregularity greater than those shown in Figure 1 and less than those seen in Figures 2 and 3. Patient 1 was the only patient with definite keratoconus in the fellow eye who did not show an early cone in the study eye (Table). Patient 2 showed topographic evidence of keratoconus in the left eye (Fig. 2) but no evidence of early involvement in the right eye (Fig. 4).

Discussion

Our results suggest that very early stages of keratoconus can be detected by using a sensitive corneal topography analysis system. The analysis system was able to detect a pattern of power distribution consistent with keratoconus in seven of nine patients in whom the diagnosis was suspected. Those who are interested in detecting pilots at risk for the development of visually disabling keratoconus before investing in their training should find the results of this study encouraging.[9] Investigators interested in better understanding the earliest stages of the natural course of cone development and those interested in determining the true incidence of unilateral keratoconus and the incidence of

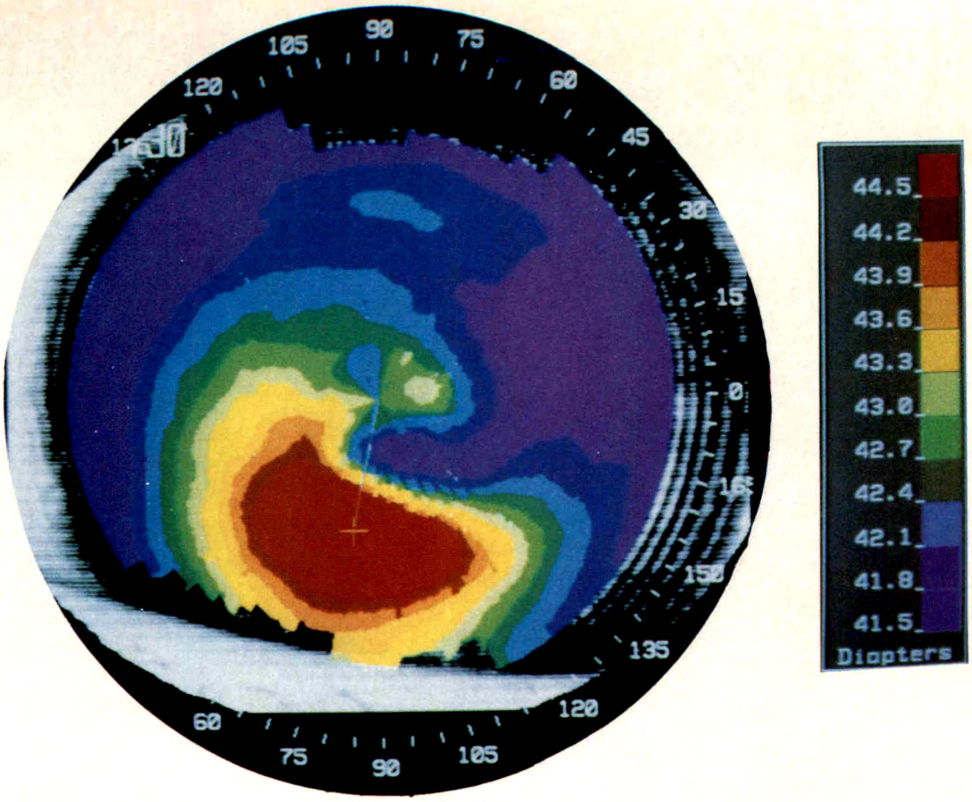

Fig. 1 (Maguire and Bourne). Computer-generated color contour map of the left eye of Patient 7. Each color represents a 0.3-diopter range of surface power. The range extends from a low of 41.5 to greater than 44.5 diopters. The area of the cone apex, identified by the red color interval, is surrounded by concentric bands of increasingly lower corneal power. Lowest corneal power is seen in the superior half of the cornea. The cursor (cross) has been placed at the cone apex.

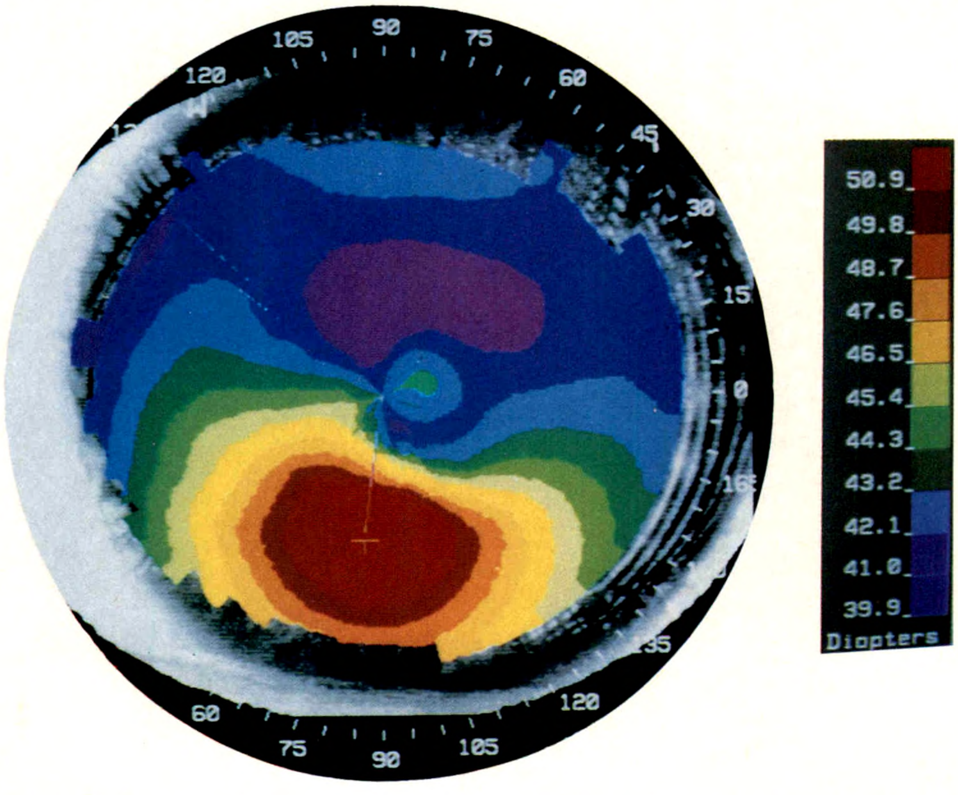

Fig. 2 (Maguire and Bourne). Contour map of the left eye of Patient 2. This cornea is more irregular. Each color interval represents a 1.1-diopter range of power. The overall range extends from 39.9 to greater than 50.5 diopters. The location of the cone apex is readily apparent. Visual acuity was 20/20, with a spectacle correction of −2.50.

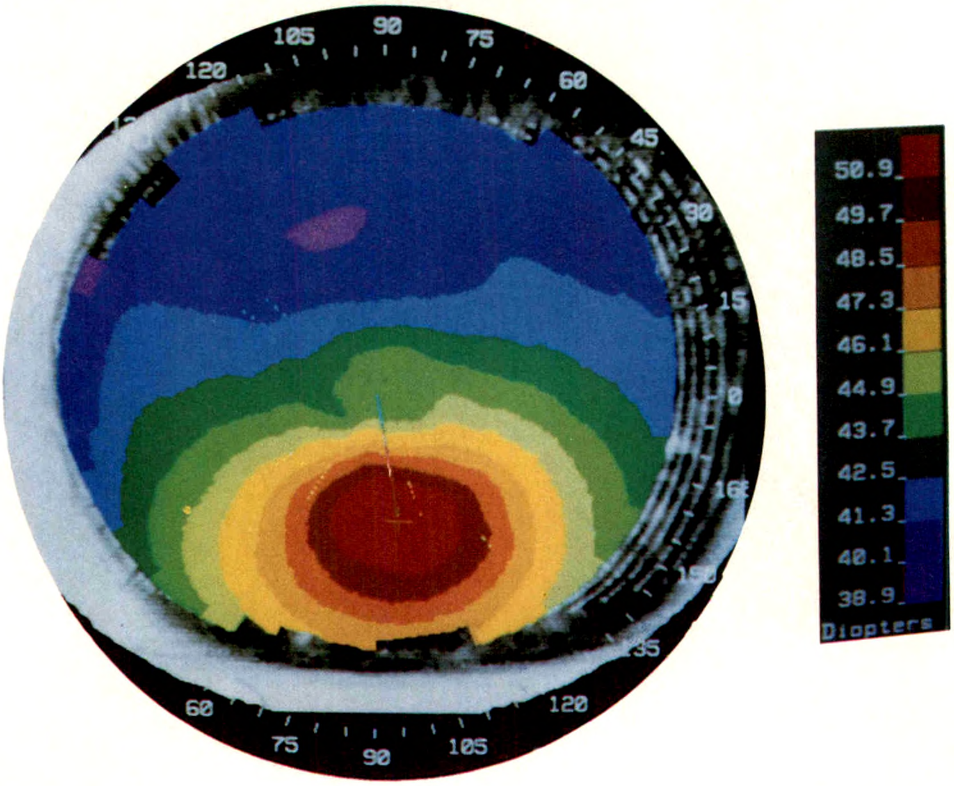

Fig. 3 (Maguire and Bourne). Contour map of the left eye of Patient 3. Each color represents a 1.2-diopter range and the overall range is 38.9 to greater than 50.9 diopters.

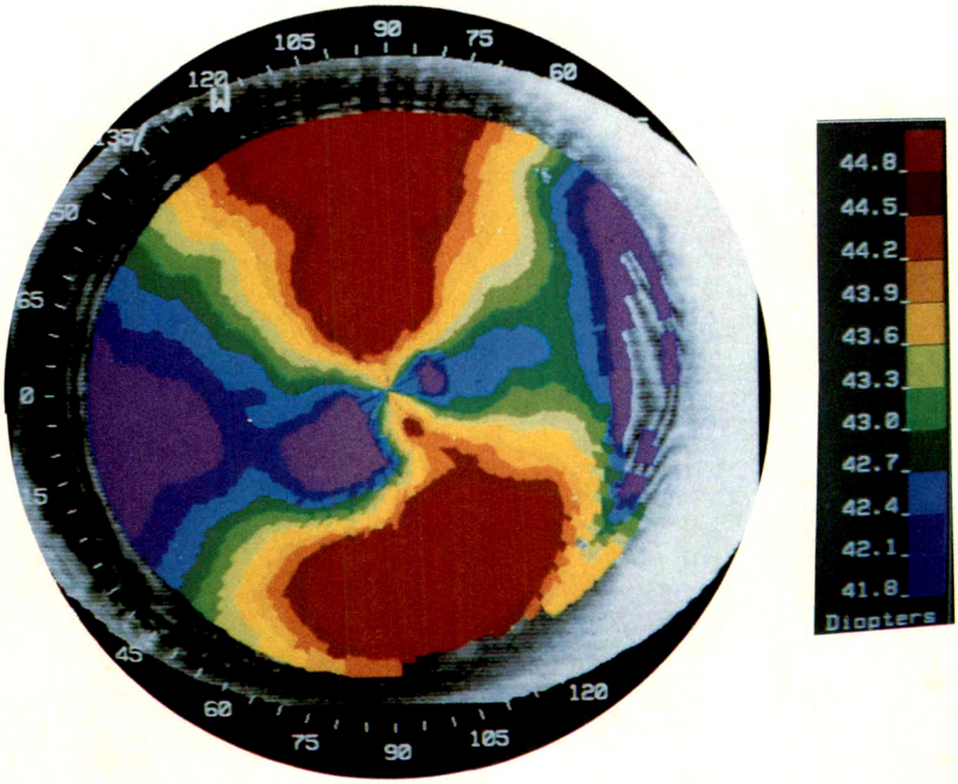

Fig. 4 (Maguire and Bourne). Contour map of the right eye of Patient 2. Each color represents a 0.3-diopter range and the overall range is 41.9 to greater than 44.8 diopters. Unlike the patient's opposite eye (Fig. 2), no topographic evidence of early keratoconus is seen.

TABLE
SUMMARY OF CORNEAL MODELING SYSTEM FINDINGS

PATIENT NO., AGE (YRS), SEX	EYE	VISUAL ACUITY WITH SPECTACLES	MANIFEST REFRACTION	TOPOGRAPHIC APEX OF CONE: DISTANCE FROM VISUAL AXIS (MM)	HEMI-MERIDIAN (DEG)	MAXIMUM POWER (D)	KERATOMETRY READING	KERATOMETER MIRE DISTORTION	SLIT-LAMP FINDINGS IN FELLOW EYE
1, 62, M	R.E.	20/20−	−1.00 +0.75 × 14	No evidence of keratoconus			43.87 × 44.12 × 98	Mild	Advanced keratoconus
2, 27, M	L.E.	20/20	−2.50	2.3	263	52.80	43.12 × 43.87 × 33	Mild	—
	R.E.	20/20	+9.75*	No evidence of keratoconus			43.00 × 45.75 × 112	None	—
3, 27, M	R.E.	20/20	−3.00	2.5	255	45.2	43.25 × 44.00 × 05	None	—
	L.E.	20/30	−2.25 +1.25 × 12	2.0	280	52.2	43.75 × 45.50 × 05	Moderate	—
4, 29, F	R.E.	20/25	−2.00	1.6	271	50.7	45.25 × 47.00 × 85	Mild	Severe keratoconus
5, 29, M	L.E.	20/20	−1.25 +2.00 × 20	2.5	245	47.6	42.25 × 45.00 × 40	None	Penetrating keratoplasty for keratoconus in 1978
6, 30, F	R.E.	20/20	−2.00 +0.75 × 166	1.3	301	45.8	43.75 × 43.87 × 163	None	Penetrating keratoplasty for keratoconus in 1985
7, 19, F	L.E.	20/20	Plano	2.1	259	44.5	43.25 × 44.00 × 90	None	Moderate

*Cataract secondary to nonpenetrating BB injury; cataract extraction age 10 years.

early keratoconus in the normal population appear to have a new tool.[10] Most importantly, topographic analysis, when used as a screening test, may help ophthalmologists interested in refractive corneal surgery avoid operating on an eye with unsuspected abnormalities in corneal curvature.

Many variables have been suggested to contribute to the lack of refractive accuracy of radial keratotomy[11] and other refractive surgical procedures.[12] Heterogeneity of the topography of the preoperative surface has only recently been suggested as one of them.[13]

It has been assumed that if the refraction, visual acuity, and keratometry readings are normal, the corneal surface is normal. The results of our study suggest otherwise. All of the patients in whom early keratoconus was identified had excellent visual acuity with spectacle correction and no slit-lamp evidence of the condition. Four of the seven patients showed no distortion of the keratometer mires. Three others showed only subtle mire distortion. These keratometric findings are not surprising because the degree of keratoconus in these eyes was not severe and the cones were not located near the two points on the corneal surface measured by the keratometer. The refractive surgeon may well ask whether some patients with poor results after radial keratotomy have had similar preoperative topographic findings.

This pilot study suggests that computer-based corneal topography analysis systems similar in design to the Corneal Modeling System are useful in the detection of early stages of keratoconus. If our findings are confirmed by other investigators, such systems should be considered for use in population-based studies to determine the true incidence of early keratoconus and to determine the degree of topographic heterogeneity in the normal population. If significant corneal irregularity is found in a relatively large percentage of normal subjects, computer-based topography analysis may become a useful preoperative screening procedure for patients interested in refractive corneal surgery.

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OPHTHALMIC MINIATURE

Being now prepared to make the section of the cornea, the surgeon, holding the knife as he would a pen, should rest the ring and middle finger of the right hand upon the temple of the patient, near the outer canthus of the eye; and place the flat part of the blade of the knife upon the surface of the cornea, and try whether he can carry the point of the instrument to the nose, without shifting the position of the fingers on the cheek. By touching the cornea, the patient is warned of the commencement of the operation. . . .

Frederick Tyrrell, A Practical Work on the Diseases of the Eye and Their Treatment, Medically, Topically, and by Operation, Vol. II. London, John Churchill, 1840, p. 396

Corneal Ulcers Associated With Disposable Hydrogel Contact Lenses

James P. Dunn, Jr., M.D., Bartly J. Mondino, M.D., Barry A. Weissman, O.D., Paul B. Donzis, M.D., and Don O. Kikkawa, M.D.

Four patients developed corneal ulcers associated with the use of disposable extended-wear hydrogel contact lenses. Bacteria were recovered from corneal ulcers in three of the patients. Three patients discarded their contact lenses after ten or more days of extended wear; the corneal ulcers in these patients developed toward the end of the wearing cycle. The fourth patient removed her contact lenses every two days for cleaning and disinfection and discarded them for a new pair on a weekly basis. Improper lens hygiene was noted in only one patient. All corneal ulcers responded to antibiotic treatment. In three patients visual acuity returned to normal, but scarring of one patient's cornea resulted in a visual acuity of 20/60.

Corneal ulcers are the most serious complication of contact lens wear. All types of contact lenses have been associated with infectious corneal ulcers, including cosmetic daily- and extended-wear hydrogel lenses,[1-6] aphakic lenses,[2,5,6] therapeutic hydrogel lenses,[4-7] cosmetic lenses used to change eye color,[8] and rigid lenses.[4-6] Corneal ulcers related to contact lens wear now form a growing percentage of all corneal ulcers.[4-6] Hydrogel contact lenses may pose a greater risk of corneal infection when used on an extended-wear rather than a daily-wear basis.[1,3,4,6,9]

The use of contact lenses may be associated with breakdown of the corneal epithelial barrier as a result of chronic hypoxic stress or manipulation of the lens during insertion or removal. Bacteria normally present in the eye or contaminating some aspect of the contact lens care system may then gain access to the corneal stroma and induce infection. Contamination may result from noncompliance with accepted principles of lens care and has been noted in contact lens wearers who are asymptomatic[10,11] or who have corneal ulcers.[1]

Disposable extended-wear hydrogel contact lenses, intended to be worn continuously for one or two weeks and then discarded, may reduce problems caused by noncompliance with good lens care since no lens cleaning or disinfection is required. Furthermore, the risks associated with aging lenses, including cracks or other surface defects that might allow microbial penetration or deposits which might facilitate bacterial adherence,[12] should be reduced. Other potential benefits include the elimination of some of the allergic and toxic complications of contact lens care products and a possible decrease in the incidence of giant papillary conjunctivitis. A premarket study of the Acuvue disposable hydrogel contact lens (etafilcon, 58% water content), consisting of 733 patients followed up for eight months of wear, found an overall complication rate of only 5.6%.[13] No corneal ulcers were noted. We examined four patients who developed corneal ulcers while wearing Acuvue disposable extended-wear contact lenses.

Case Reports

Case 1

A 40-year-old woman had been using disposable hydrogel contact lenses on an extended-wear basis for three months. She replaced the lenses every 11 to 14 days. Before using disposable lenses, she had used daily-wear hydrogel lenses sporadically for six years. She changed

Accepted for publication May 8, 1989.

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to disposable contact lenses because of their greater convenience. She had worn her current lenses for 12 days and noticed pain and redness in her right eye that progressed overnight to severe pain and photophobia.

On examination, visual acuity was R.E.: 20/25 and L.E.: 20/15. The right eye showed mild edema of the eyelids. Slit-lamp examination showed moderate conjunctival hyperemia and a 1-mm corneal epithelial defect overlying a 2.5-mm stromal infiltrate in the midperiphery at the 7:00 o'clock position. There was surrounding stromal and epithelial edema, which spared the visual axis. The anterior chamber showed 1+ cells and flare. Cultures of the right cornea grew coagulase-negative *Staphylococcus*.

She was treated with hourly topical tobramycin 15 mg/ml and cefazolin 50 mg/ml. Within 24 hours the patient's symptoms improved substantially, and the epithelium was intact. After five days, topical dexamethasone sodium phosphate 0.1% was added to the fortified antibiotic regimen to reduce stromal scarring. All topical medications were tapered and then discontinued over a three-week period. A faint stromal scar persisted, but best-corrected visual acuity was 20/15.

Case 2

A 34-year-old woman was referred because of a two-day history of pain, redness, and decreased vision in the right eye. She had worn daily-wear hydrogel contact lenses for seven years until changing to disposable extended-wear hydrogel lenses three months before examination. She wore the disposable lenses on an extended-wear basis for a two-week cycle and noticed discomfort after 11 days of wear with her latest pair.

On examination, visual acuity was R.E.: 20/20 and L.E.: 20/15. Slit-lamp examination of the right eye demonstrated mild conjunctival hyperemia and a 2-mm peripheral corneal infiltrate with a 0.5-mm overlying epithelial defect at the 5:00 o'clock position. Trace cells and flare were seen in the anterior chamber. Corneal cultures showed no growth at 48 hours.

The patient was treated with hourly topical tobramycin 0.3% and bacitracin zinc-neomycin sulfate-polymyxin B sulfate while awake. After 24 hours, the epithelial defect was healed. The topical antibiotics were tapered to every two hours. After four days her treatment regimen was changed to combined tobramycin 0.3%/dexamethasone 0.1% four times each day. One week later, the infiltrate had virtually resolved, and the medication was tapered and discontinued over four days. Two weeks later only a faint opacity remained, and best-corrected visual acuity was 20/15.

Case 3

A 27-year-old woman had worn disposable hydrogel contact lenses for six months without problems but admitted to wearing them longer than the recommended two-week extended-wear period on occasion. The patient also admitted to infrequent handwashing before handling her lenses. Her fingernails were long, and she believed she may have scratched her eyes on occasion. Two days before our examination, she noticed pain in her right eye just before replacing her two-week-old contact lenses. The pain worsened over the next few hours, and she was seen in a general emergency room where a diagnosis of sterile corneal infiltrate was made. She was treated with topical sulfacetamide 10%, cyclopentolate 1%, and a pressure patch. She returned 36 hours later with severe pain, tearing, and discharge and was referred for examination.

Visual acuity was R.E.: 20/60 and L.E.: 20/20. Slit-lamp examination of the right eye showed a crescent-shaped 1 × 3-mm stromal infiltrate with an overlying 3 × 3-mm epithelial defect in the visual axis. The anterior chamber had 4+ cells and flare and a small hypopyon. A bottle of artificial tears used several times each day was noted to have mascara crystals on the tip. Cultures of the tip and the solution itself showed no bacterial or fungal growth. Cultures of the corneal ulcer grew *Pseudomonas aeruginosa*.

The patient was treated with hourly topical tobramycin 15 mg/ml and cefazolin 50 mg/ml. After 12 hours of antibiotic treatment, her visual acuity decreased to counting fingers at 2 feet, and the infiltrate had enlarged (Fig. 1). The ulcer then improved over the next 24 hours. The patient remained hospitalized for five days while being treated with hourly topical antibiotics. After discharge, the antibiotics were tapered slowly. The epithelium was intact two weeks later. The stromal opacity had decreased in size, but stromal thinning was noted. Best-corrected visual acuity was 20/60.

Case 4

A 22-year-old woman had worn extended-wear hydrogel contact lenses for four years and

Fig. 1 (Dunn and associates). Case 3, right eye. Central corneal ulcer caused by *Pseudomonas aeruginosa*.

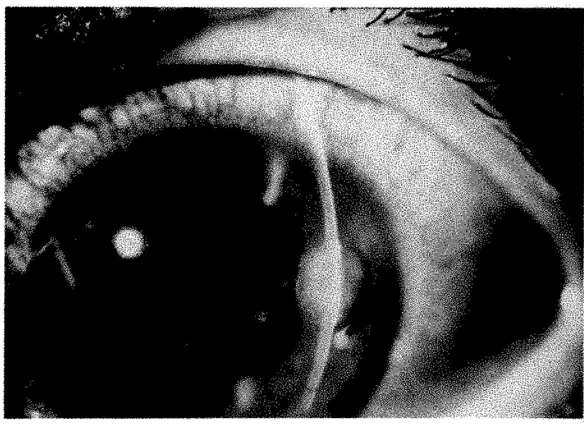

Fig. 2 (Dunn and associates). Case 4, left eye. Paracentral corneal ulcer.

had switched to disposable contact lenses seven months before examination. She wore the disposable hydrogel contact lenses for two days at a time, removed them for cleaning and overnight disinfection with a hydrogen peroxide care system, and discarded them weekly. Two days before our examination, she developed pain and tearing in her left eye after two days of contact lens wear. She was seen by her ophthalmologist and found to have bilateral corneal ulcers. Treatment with gentamicin 0.3% four times each day and bacitracin zinc-polymyxin B sulfate ointment at night in both eyes was ineffective, and she was referred for examination.

Visual acuity was R.E.: 20/40 and L.E.: 20/50. Slit-lamp examination of the right eye showed two 1-mm round stromal infiltrates, one located paracentrally and one peripherally, each with an overlying epithelial defect. Trace anterior chamber cells and flare were noted. The left eye had a round 2.5-mm corneal epithelial defect over a stromal infiltrate in the nasal midperiphery (Fig. 2). The anterior chamber showed 1+ cells and flare. Corneal cultures from the left eye grew *Propionibacterium acnes*.

The patient was treated hourly with topical tobramycin 15 mg/ml and cefazolin 50 mg/ml in both eyes. Over the next four days, the stromal infiltrates regressed and the epithelial defects healed. The antibiotic eyedrops were tapered and then discontinued over several weeks. Her best-corrected visual acuity improved to 20/20 in both eyes. Stromal scars were faintly visible in the right cornea. A large stromal opacity with associated thinning was present in the left cornea.

Discussion

The development of microbial corneal ulcers in contact lens wearers probably involves both disruption of the epithelial surface and microbial invasion of the stroma. Bacteria can adhere to hydrogel contact lenses[12] and may then gain access to the corneal stroma after epithelial trauma.[14] Such trauma may be an inevitable consequence of all contact lens use, especially during extended wear. All available hydrogel contact lenses cause hypoxic changes in the corneal epithelium when used on an extended-wear basis.[15] These changes include reduced corneal sensitivity, decreased epithelial mitosis and adhesion, premature desquamation of epithelial cells, and epithelial microcystic edema. The disposable hydrogel contact lenses used by all patients in this study were similar in water content and thickness, and therefore oxygen transmissibility, to other reusable hydrogel extended-wear contact lenses.

The theoretical advantage of disposable contact lenses lies in a reduction of lens contamination associated with noncompliance in contact lens care. Proper contact lens care includes handwashing before any lens manipulation, appropriate use of an approved contact lens care system, adherence to recommended contact lens-wearing schedule, and absence of mi-

crobial contamination of contact lens cases and solutions. Noncompliance has been found in about 50% of asymptomatic contact lens users[10,11] and in patients with corneal ulcers associated with contact lens wear.[1] It has also been noted that soft contact lenses develop deposits with time that cannot be removed completely even by professional contact lens cleaning.[16] Bacteria may adhere to these deposits.[12] By eliminating the use of care systems and shortening the use of the lens, it is the goal of manufacturers of disposable hydrogel lenses to improve compliance, reduce deposit formation, and ensure that all inserted contact lenses are clean and sterile. The risk of corneal ulcers should thereby be reduced. Indeed, corneal ulcers were not reported in the initial evaluation of disposable contact lens wear.[13]

There remain, however, potential complications associated with any type of extended-wear hydrogel contact lens that disposability may not solve. The increased cost of disposable contact lenses[13] may induce some patients to use them longer than the suggested period. While being worn any contact lens is subject to contamination from environmental pollutants, cosmetics (such as eyeliner), and eyedrops. These sources of contamination may play a role in the development of corneal ulcers, since one study found that 12 of 29 extended-wear patients with corneal ulcers had no identifiable break in compliance.[1]

Our patients showed many of the potential sources of contamination in disposable contact lens wear. Patient 3 did not usually wash her hands before removing or inserting her lenses, thus negating the advantage of inserting a sterile contact lens at each lens change. She also admitted to using the lenses for longer than two weeks on occasion, which could aggravate chronic corneal hypoxia. She had long fingernails, which may have contributed to epithelial trauma. She improperly used a topical lubricant, as evidenced by mascara deposits on the bottle tip (although cultures were negative). Finally, she inserted a new contact lens onto an already painful eye.

Patient 4 represents a special situation, since she disposed of her lenses on a weekly basis, but removed them every two days for cleaning and disinfection. Although such use reintroduces the complications associated with traditional contact lens care, this type of regimen has been recommended as a compromise between the risks of corneal hypoxia associated with weekly contact lens wear and the problems related to care solutions. It has also been shown that more frequent replacement of reusable traditional extended-wear hydrogel contact lenses may reduce the incidence of corneal ulcers.[17]

Patients 1 and 2 did not have any obvious risk factors for corneal ulcers other than extended wear. Both patients reported compliance with the recommended wear schedule and washed their hands before lens manipulation.

Pseudomonas is the most common pathogen in contact lens-related corneal ulcers, followed by *Staphylococcus*.[4-6] These bacteria were found in two of the corneal ulcers in this study. Cultures are negative in approximately one half of all contact lens-related corneal ulcers.[3-5] Culture results may be affected by previous treatment with antibiotics. However, all four patients described here demonstrated epithelial defects, stromal infiltration, anterior chamber reaction, and pain characteristic of infectious keratitis.[18]

We are concerned that the concept of disposability may give patients and practitioners a false sense of safety regarding extended wear, and that the increased cost of disposable contact lenses may encourage patients to wear them longer than recommended. A case of keratitis associated with disposable hydrogel contact lenses was reported recently, but no bacteria were isolated from the cornea.[19] Wearers of disposable extended-wear hydrogel contact lenses are at risk for the development of bacterial corneal ulcers.

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Clinical Indications for and Procedures Associated With Penetrating Keratoplasty, 1983–1988

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We reviewed the preoperative clinical indications and associated surgical procedures for 2,299 penetrating keratoplasties performed at our institution from 1983 through 1988. Pseudophakic bullous keratopathy was the most common indication overall, accounting for 526 cases (23%). A marked increase was noted in the incidence of pseudophakic bullous keratopathy as an indication for penetrating keratoplasty beginning in 1985. The association of anterior chamber intraocular lenses in eyes with pseudophakic bullous keratopathy undergoing penetrating keratoplasty increased from 19 of 43 cases (44%) in 1983 to 79 of 108 cases (73%) in 1988. The incidence of intraocular lens exchange at the time of penetrating keratoplasty in cases of pseudophakic bullous keratopathy increased from six of 43 (14%) in 1983 to 63 of 108 (58%) in 1988.

Other major indications for penetrating keratoplasty included Fuchs' dystrophy (375 cases, 16%), keratoconus (348 cases, 15%), aphakic bullous keratopathy (331 cases, 14%), and regraft (233 cases, 10%). Cataract extraction, with or without intraocular lens implantation, was combined with penetrating keratoplasty in 397 of 1,532 phakic eyes (26%). The incidence of triple procedure (penetrating keratoplasty, cataract extraction, and intraocular lens implantation) increased from 27 of 248 phakic eyes (11%) in 1983 to 68 of 258 phakic eyes (26%) in 1988.

THE NUMBER OF penetrating keratoplasties performed in the United States has increased from over 15,000 in 1981 to over 36,000 in 1988 (Activity Reports, 1981 and 1988, Eye Bank Association of America). Continued improvement in surgical technique, instrumentation, donor tissue preservation, and pharmacologic advances have made it a highly successful surgical procedure. Previous reports have documented trends in changing indications for penetrating keratoplasty since the early 1940s.[1-3] We reviewed the clinical indications for 2,299 penetrating keratoplasties performed between 1983 and 1988 as well as the trends in associated procedures combined with penetrating keratoplasty, including cataract extraction, intraocular lens implantation, and management of intraocular lenses in cases of pseudophakic bullous keratopathy.

Material and Methods

We reviewed the charts of all patients who underwent penetrating keratoplasty at our institution during the six-year period from Jan. 1, 1983 through Dec. 31, 1988. Information obtained included date of surgery, patient age, surgeon, and the preoperative clinical diagnosis for which penetrating keratoplasty was performed.

Preoperative clinical diagnostic indications for penetrating keratoplasty were divided into 17 categories (Table 1). In most cases, only one clinical diagnosis was present. However, in patients with more than one diagnosis, the following priority guidelines were used to assure uniform categorization. The category of regraft was given the highest priority. In other words, if the eye undergoing penetrating keratoplasty had had a previous transplant, then it fell into the regraft category despite the presence of any other diagnosis or condition. Similarly, pseudophakic and aphakic bullous keratopathy were given a higher priority level than Fuchs' dystrophy. For example, cases of corne-

Accepted for publication April 25, 1989.
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TABLE 1
CLINICAL INDICATIONS FOR PENETRATING KERATOPLASTY BY YEAR

INDICATION	1983	1984	1985	1986	1987	1988	TOTAL
Pseudophakic bullous keratopathy	43 (12.1%)	60 (15.3%)	98 (25.2%)	98 (26.3%)	119 (30.0%)	108 (27.4%)	526 (22.9%)
Fuchs' dystrophy	56 (15.8%)	71 (18.1%)	57 (14.7%)	62 (16.6%)	54 (13.6%)	75 (19.0%)	375 (16.3%)
Keratoconus	59 (16.7%)	77 (19.6%)	57 (14.7%)	59 (15.8%)	48 (12.1%)	48 (12.2%)	348 (15.1%)
Aphakic bullous keratopathy	74 (20.9%)	57 (14.5%)	55 (14.1%)	49 (13.1%)	51 (12.8%)	45 (11.4%)	331 (14.4%)
Regraft	32 (9.0%)	42 (10.7%)	35 (9.0%)	42 (11.3%)	41 (10.3%)	41 (10.4%)	233 (10.1%)
Virus	22 (6.2%)	17 (4.3%)	16 (4.1%)	16 (4.3%)	18 (4.5%)	12 (3.0%)	101 (4.4%)
Interstitial keratitis	11 (3.1%)	18 (4.6%)	13 (3.3%)	15 (4.0%)	13 (3.3%)	18 (4.6%)	88 (3.8%)
Trauma	7 (2.0%)	12 (3.1%)	15 (3.9%)	7 (1.9%)	10 (2.5%)	7 (1.8%)	58 (2.5%)
Ulcerative conditions	9 (2.5%)	12 (3.1%)	7 (1.8%)	9 (2.4%)	12 (3.0%)	9 (2.3%)	58 (2.5%)
Scarring	10 (2.8%)	7 (1.8%)	10 (2.6%)	5 (1.3%)	12 (3.0%)	5 (1.3%)	49 (2.1%)
Non-Fuchs' dystrophy	7 (2.0%)	4 (1.0%)	15 (3.9%)	1 (0.3%)	4 (1.0%)	8 (2.0%)	39 (1.7%)
Corneal edema	4 (1.1%)	2 (0.5%)	4 (1.0%)	5 (1.3%)	7 (1.8%)	6 (1.5%)	28 (1.2%)
Miscellaneous	1 (0.3%)	6 (1.5%)	2 (0.5%)	0 (0.0%)	3 (0.8%)	1 (0.3%)	13 (0.6%)
Chemical burn	1 (0.3%)	3 (0.8%)	2 (0.5%)	3 (0.8%)	1 (0.3%)	1 (0.3%)	11 (0.5%)
Degeneration	3 (0.8%)	1 (0.3%)	2 (0.5%)	0 (0.0%)	1 (0.3%)	4 (1.0%)	11 (0.5%)
Congenital	1 (0.3%)	2 (0.5%)	1 (0.3%)	2 (0.5%)	0 (0.0%)	3 (0.8%)	9 (0.4%)
Unknown	14 (4.0%)	1 (0.3%)	0 (0.0%)	0 (0.0%)	3 (0.8%)	3 (0.8%)	21 (0.9%)
Total	354 (100.0%)	392 (100.0%)	389 (100.0%)	373 (100.0%)	397 (100.0%)	394 (100.0%)	2,299 (100.0%)

al edema associated with previous cataract surgery and endothelial dystrophy were placed in the pseudophakic or aphakic bullous keratopathy categories rather than the Fuchs' dystrophy category. The categories of corneal edema and scarring include only those eyes in which these conditions were idiopathic or the result of causes other than those listed in any other category.

In cases of pseudophakic bullous keratopathy, the type of intraocular lens was recorded. In cases of regraft, the previous underlying diagnosis was noted when available. Information was also obtained regarding the incidence of combined penetrating keratoplasty and cataract extraction with and without implantation of an intraocular lens. Management of previously implanted intraocular lenses in applicable cases of pseudophakic bullous keratopathy was also recorded.

Results

A total of 2,299 penetrating keratoplasties were performed between 1983 and 1988. An average of 383 penetrating keratoplasties were performed each year, ranging from 354 in 1983 to 397 in 1987 (Table 1). The average age of patients undergoing penetrating keratoplasty was 62 years (range, 3 months to 96 years). There was no significant change in age characteristics during the study period. Patients were operated on by 18 surgeons. However, 1,995 (87%) of the penetrating keratoplasties were performed by three of these surgeons.

Pseudophakic bullous keratopathy was the most common indication, accounting for 526 cases (23%) of all penetrating keratoplasties performed (Table 1). This category includes all cases of corneal edema associated with previous cataract surgery in which an intraocular lens had been implanted either primarily or secondarily, whether or not the implant was still in situ or had been explanted previously.

A marked change was noted over the study period with respect to the number of penetrating keratoplasties performed for pseudophakic bullous keratopathy. In the first and second years of the study, it was only the fourth and third most common indication, respectively. However, in the final four years, 1985 through 1988, it was the most common indication, accounting for over one quarter of the penetrating keratoplasties each year.

Of the 526 cases of pseudophakic bullous keratopathy, 331 (63%) were associated with

TABLE 2
INTRAOCULAR LENS TYPE IN PSEUDOPHAKIC BULLOUS KERATOPATHY BY YEAR

LENS TYPE	1983	1984	1985	1986	1987	1988	TOTAL
Anterior chamber	19 (44.2%)	30 (50.0%)	56 (57.1%)	64 (65.3%)	83 (69.7%)	79 (73.1%)	331 (62.9%)
Iris fixated	16 (37.2%)	20 (33.3%)	29 (29.6%)	11 (11.2%)	13 (10.9%)	10 (9.3%)	99 (18.8%)
Posterior chamber	7 (16.3%)	8 (13.3%)	12 (12.2%)	23 (23.5%)	19 (16.0%)	13 (12.0%)	82 (15.6%)
Unknown	1 (2.3%)	2 (3.4%)	1 (1.0%)	0 (0.0%)	4 (3.4%)	6 (5.6%)	14 (2.6%)
Total	43 (100.0%)	60 (100.0%)	98 (100.0%)	98 (100.0%)	119 (100.0%)	108 (100.0%)	526 (100.0%)

anterior chamber intraocular lenses (Table 2). This association showed a constant increase in frequency from 19 of 43 cases (44%) in 1983 to 79 of 108 cases (73%) in 1988. Iris-fixated intraocular lenses accounted for 99 of the total 526 cases (19%), but showed a gradual decrease in frequency from 16 of 43 cases (37%) in 1983 to ten of 108 cases (9%) in 1988. Posterior chamber intraocular lenses were found in 82 of the 526 eyes (16%) over the six-year period.

Management of the intraocular lens in eyes undergoing penetrating keratoplasty for pseudophakic bullous keratopathy changed significantly during the study period (Table 3). Of 43 such eyes in 1983, the intraocular lens was removed in only five (12%) and it was exchanged in only six (14%). However, in 1988, during which 108 transplants were performed for pseudophakic bullous keratopathy, 11 (10%) of the intraocular lenses were removed and 63 (58%) were exchanged.

Fuchs' dystrophy, keratoconus, and aphakic bullous keratopathy as indications for penetrating keratoplasty all followed pseudophakic bullous keratopathy in frequency, accounting for 375 (16%), 348 (15%), and 331 (14%) of cases, respectively. Fuchs' dystrophy showed little significant change over the study period. Keratoconus, however, demonstrated a tendency to decrease in frequency from 77 of 392 cases (20%) in 1984 to 48 of 394 cases (12%) in 1988. Aphakic bullous keratopathy demonstrated a similar decreasing tendency from 74 of 354 cases (21%) in 1983 to 45 of 394 cases (11%) in 1988.

Regraft was the fifth most common indication for penetrating keratoplasty in the series, accounting for 233 (10%) of the cases. No significant change was noted in this percentage over the six years. In these regraft cases, aphakic and pseudophakic bullous keratopathy were found to be the most common clinical diagnoses for the previous penetrating keratoplasty, accounting for 46 cases (20%) and 44 cases (19%), respectively (Table 4).

Viral disease, which included both herpes simplex keratitis (97 cases) and herpes zoster ophthalmicus (four cases), accounted for 101 (4%) of cases overall and decreased in frequency from 22 of 354 cases (6%) in 1983 to 12 of 394 cases (3%) in 1988.

Combined, the six categories of pseudophakic bullous keratopathy, Fuchs' dystrophy, keratoconus, aphakic bullous keratopathy, regraft, and viral disease accounted for 1,914 of the 2,299 penetrating keratoplasties performed (83%). Other less common categories are listed in Table 1. Scarring, including interstitial kera-

TABLE 3
INTRAOCULAR LENS MANAGEMENT IN CASES OF PSEUDOPHAKIC BULLOUS KERATOPATHY BY YEAR (% OF PSEUDOPHAKIC BULLOUS KERATOPATHY CASES)

LENS MANAGEMENT	1983	1984	1985	1986	1987	1988	TOTAL
Intraocular lens removal	5 (11.6%)	8 (13.3%)	11 (11.2%)	17 (17.3%)	14 (11.8%)	11 (10.2%)	66 (12.5%)
Intraocular lens exchange	6 (14.0%)	15 (25.0%)	30 (30.6%)	25 (25.5%)	61 (51.3%)	63 (58.3%)	200 (38.0%)
Intraocular lens reposition	1 (2.3%)	1 (1.7%)	4 (4.1%)	2 (2.0%)	1 (0.8%)	1 (0.9%)	10 (1.9%)
Intraocular lens unchanged	31 (72.1%)	36 (60.0%)	53 (54.1%)	54 (55.1%)	43 (36.1%)	33 (30.6%)	250 (47.5%)
Total	43 (100.0%)	60 (100.0%)	98 (100.0%)	98 (100.0%)	119 (100.0%)	108 (100.0%)	526 (100.0%)

TABLE 4
PREVIOUS DIAGNOSIS IN REGRAFTS

DIAGNOSIS	TOTAL
Aphakic bullous keratopathy	46
Pseudophakic bullous keratopathy	44
Fuchs' dystrophy	22
Regraft	22
Keratoconus	20
Virus	15
Interstitial keratitis	13
Unknown	12
Trauma	11
Non-Fuchs' dystrophy	9
Chemical burn	5
Ulcerative conditions	4
Corneal edema	4
Miscellaneous	3
Degeneration	2
Scarring	1
Congenital	0
Total	233

titis and trauma, accounted for 195 cases (8%). Sterile and infectious ulcerative conditions were indications for penetrating keratoplasty in 58 cases (3%) and non-Fuchs' corneal dystrophies accounted for 39 cases (2%).

Penetrating keratoplasty was combined with cataract extraction in 397 of 1,532 phakic eyes (26%) (Table 5). Within this group there was a significant increase in the number of triple procedures (combined penetrating keratoplasty, cataract extraction, and intraocular lens implantation) performed, from 27 of 248 cases (11%) in 1983 to 68 of 258 cases (26%) in 1988. This was accompanied by a concurrent decrease in combined cases without intraocular lens implantation, from 34 of 248 cases (14%) in 1983 to five of 258 cases (2%) in 1988.

Discussion

We reviewed the clinical indications and associated procedures in 2,299 penetrating keratoplasties performed at our institution over a six-year period from 1983 to 1988. Other reports on changing indications for penetrating keratoplasty have shown that corneal edema after cataract surgery has been the leading indication for penetrating keratoplasty since the mid 1970s.[1-3] This trend has continued as the combined categories of pseudophakic and aphakic bullous keratopathy accounted for 37% of the cases in our series.

Pseudophakic bullous keratopathy was the single most common indication for penetrating keratoplasty in our study, accounting for 23% of all the transplants done. However, in contrast to Robin and associates[3] who found pseudophakic bullous keratopathy to be the leading indication since 1979, in our study it has occupied this position only since 1985. Before that time it was the third or fourth most common indication, after keratoconus, Fuchs' dystrophy, and aphakic bullous keratopathy (which was the leading indication for penetrating keratoplasty in 1983, the first year of the study).

Most cases of pseudophakic bullous keratop-

TABLE 5
CATARACT EXTRACTION PROCEDURES ASSOCIATED WITH PENETRATING KERATOPLASTY BY YEAR
(% OF PHAKIC PENETRATING KERATOPLASTIES)

ASSOCIATED PROCEDURE	1983	1984	1985	1986	1987	1988	TOTAL
Triple procedure	27 (10.9%)	50 (17.3%)	44 (17.7%)	52 (21.5%)	59 (23.9%)	68 (26.4%)	300 (19.6%)
Cataract extraction without intraocular lens implant	34 (13.7%)	18 (6.2%)	16 (6.5%)	14 (5.8%)	10 (4.0%)	5 (1.9%)	97 (6.3%)
No cataract extraction	187 (75.4%)	221 (76.5%)	188 (75.8%)	176 (72.7%)	178 (72.1%)	185 (71.7%)	1,135 (74.1%)
Total	248 (100.0%)	289 (100.0%)	248 (100.0%)	242 (100.0%)	247 (100.0%)	258 (100.0%)	1,532 (100.0%)

athy (64%) were associated with anterior chamber intraocular lenses (Table 2). This association is consistent with the popularity of anterior chamber intraocular lenses in the early 1980s, particularly the closed-loop styles, which have since been shown to cause delayed corneal edema.[4,5] The incidence of associated anterior chamber intraocular lenses grew steadily over the six-year period, from 44% of cases in 1983 to 73% of cases in 1988. This persistent increase, despite the large shift from anterior chamber to posterior chamber intraocular lenses in the mid 1980s[6] emphasizes the continued impact of anterior chamber intraocular lenses on corneal disease.

The approach to management of the intraocular lens at the time of penetrating keratoplasty in cases of pseudophakic bullous keratopathy changed significantly during the study period (Table 3). In 1983 the intraocular lens was removed or exchanged at the time of penetrating keratoplasty in 26% of cases. By 1988, this figure had increased to 68%. This change in management resulted largely from the high incidence of graft failure found in eyes in which anterior chamber intraocular lenses had been left in place during penetrating keratoplasty.[7]

As in previous reports, Fuchs' dystrophy and keratoconus continue to represent significant indications for penetrating keratoplasty, accounting for 16% and 15% of cases, respectively. The incidence of penetrating keratoplasties for keratoconus showed a gradual decrease over the study period from 17% in 1983 to 12% in 1988. This is probably because of the advances in management of this condition with rigid gas-permeable contact lenses.

Regraft, which was the most common indication for penetrating keratoplasty before the mid 1970s,[1] accounted for 10% of penetrating keratoplasties in our study and demonstrated little change in frequency throughout the six-year period. This percentage is less than in other more recent reports on the indications for penetrating keratoplasty.[2,3] In the current study, three surgeons performed 87% of the 2,299 procedures, which contrasts with 151 surgeons for 710 procedures[2] and 47 surgeons for 497 procedures[3] in reports in which the incidence of penetrating keratoplasty for graft failure was 15%.

Viral disease as an indication for penetrating keratoplasty has shown a gradual decrease in frequency over the past six years, consistent with the marked improvement in the recognition and medical treatment of herpes simplex keratitis. Although little change occurred in the incidence of cataract extraction combined with penetrating keratoplasty over the study period, there was within this group a significant increase in the number of triple procedures performed (Table 5).

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Familial Congenital Cornea Guttata With Anterior Polar Cataracts

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We examined 21 members of a family with a syndrome of cornea guttata and anterior polar cataracts. Twelve members had both ocular abnormalities. An affected woman underwent penetrating keratoplasty at age 28 years. Light microscopy of the corneal button showed changes consistent with cornea guttata and corneal edema. The combination of cornea guttata and anterior polar cataracts appears to form a well-defined ocular syndrome that is inherited in an autosomal dominant fashion.

In 1951 Dohlman described a large Swedish family with autosomal dominant cornea guttata and anterior polar cataracts.[1] We examined 21 members of a family of presumed Scandinavian origin with the same syndrome (Fig. 1). Twelve members were found to have cornea guttata and anterior polar cataracts. Three additional patients were presumably affected but were not available for examination. The family's ancestors had immigrated to the United States in the 17th century from Ireland, where they had settled in the 13th century after moving from Scandinavia.

Case Reports

Proband (V-10)

This woman had undergone surgery for developmental cataracts at age 21 and 28 years in the left and right eyes, respectively. Her best postoperative visual acuity was R.E.: 20/20 and L.E.: 20/30. She had typical cornea guttata in both eyes. Shortly after cataract extraction in the right eye she developed corneal edema in the left eye, which had been operated on seven years earlier. She underwent successful penetrating keratoplasty in the left eye. At age 31 years she underwent corneal transplantation in the right eye. Seven years later, at age 38 years, she had a rejection episode in the right eye. The episode was managed successfully with topical corticosteroid therapy.

Histopathologic study of the right corneal button showed changes typical of classic cornea guttata (Fig. 2). There was epithelial edema with an otherwise unremarkable stroma. Descemet's membrane was markedly thickened with multiple excrescences. The corneal endothelium appeared to be degenerated, although fixation and tissue handling artifacts could not be ruled out.

Other Family Members

All affected patients (Fig. 1, Table) had both components of the syndrome and had visual acuity of 20/50 or better. No other ocular abnormalities or significant errors of refraction were present. Corneal changes were more severe in older patients, and in a few patients the changes had been documented to increase in severity with time. Three patients (including the proband) underwent cataract surgery for developmental or presenile cataracts, with excellent postoperative visual results. Patient IV-5 was operated on at age 32 years and patient IV-6 was operated on at ages 12 and 19 years on her right and left eyes, respectively.

Discussion

We believe that the present family has the same autosomal dominant syndrome of cornea guttata and anterior polar cataracts as the family described by Dohlman in 1951.[1] The probable Scandinavian origin of the present family sug-

Accepted for publication April 27, 1989.
From the Center for Sight, Georgetown University Medical Center, Washington, D.C. This study was presented at the 15th meeting of the Ophthalmic Genetics Study Club, Las Vegas, Oct. 8, 1988.
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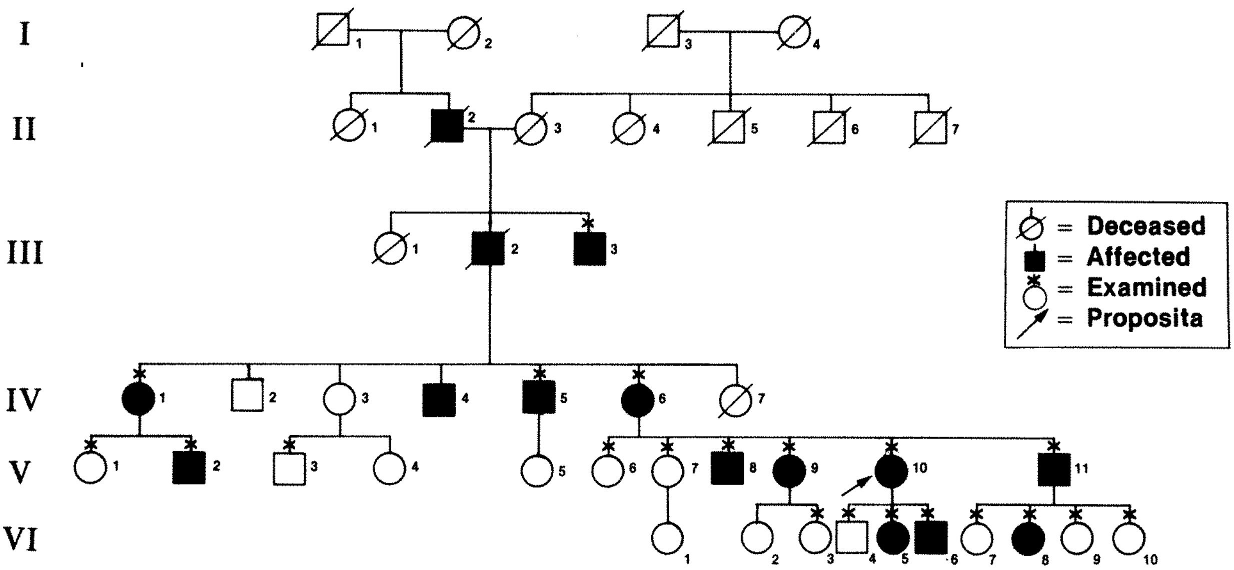

Fig. 1 (Traboulsi and Weinberg). Pedigree of a six-generation family with cornea guttata and anterior polar cataracts.

gests that the syndrome in both families may be caused by the same gene. In Dohlman's study, affected individuals had classic cornea guttata documented as early as 10 years of age and anterior polar cataracts of variable severity.

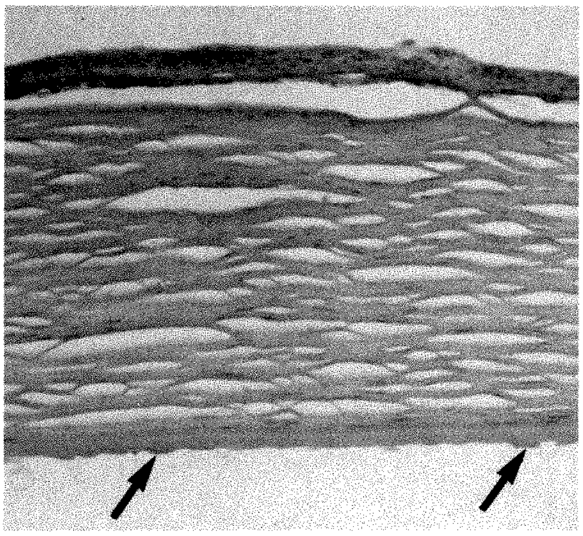

Fig. 2 (Traboulsi and Weinberg). Section of corneal button from Patient V-10 (proband) showing epithelial edema, unremarkable stroma, and a markedly thickened Descemet's membrane with multiple excrescences (arrows). The endothelium is not evident in this section but appears degenerated on other sections (hematoxylin and eosin, ×40).

The corneal changes were bilateral, equally advanced in both eyes, and were variable in severity between family members. In all patients, however, the central cornea was more severely affected than the periphery. Anterior polar cataracts ranged in size from a small parenchymal opacity to disks as large as 3 mm in diameter or cones involving the lens capsule. The fetal nucleus was spared in all patients. One patient underwent cataract surgery at age 70 years and another in his fourth or fifth decade (age not specified). Two patients had cornea guttata but no anterior polar cataracts; one of these two patients had a posterior polar cataract. Cataracts were diagnosed as early as 6 months of age in one patient, but were not apparent until age 3 or 4 years in other patients. Dohlman[1] proposed that the polar cataracts were not necessarily present at birth but appeared in the first few years of life. Corneal changes developed in the first decade of life and progressed with age. Dohlman[1] ascribed early visual impairment to large polar cataracts, and later visual impairment to progression of cataracts or increasing severity of corneal disease. An autosomal dominant mode of inheritance was evident in the family described by Dohlman, with vertical and male to male transmission of the condition, equal affection of males and females, and absence of parental consanguinity. Both ocular components of the syndrome occurred together in almost all cases

TABLE
OCULAR FINDINGS AT LAST EXAMINATION IN PATIENTS WITH CORNEA GUTTATA AND ANTERIOR POLAR CATARACTS

PATIENT (PEDIGREE NO.)	AGE AT LAST EXAMINATION (YRS)	VISUAL ACUITY R.E.	VISUAL ACUITY L.E.	REMARKS
III-3	—*	20/40	20/40	Nuclear sclerosis in both eyes
IV-1	37	20/50	20/25	—
IV-5	49	20/50	20/40	Cataract surgery in both eyes
IV-6	51	20/30	20/30	Cataract surgery in both eyes
V-2	13	20/20	20/20	—
V-8	26	20/40	20/40	—
V-9	29	20/30	20/30	—
V-10 (proband)	38	20/20	20/30	Cataract surgery and keratoplasty in both eyes
V-11	33	20/20	20/20	—
VI-5	11	20/25	20/25	—
VI-6	13	20/40	20/30	—
VI-8	11	20/20	20/20	—

*Deceased patient examined elsewhere. Information obtained from medical record.

and thus are best attributed to the effects of the same gene. Dohlman[1] postulated that both ocular abnormalities resulted from a disturbance in embryogenesis during the eighth week of gestation when the anterior chamber is forming and the posterior surface of the cornea is separating from the anterior surface of the lens.

Affected individuals in the present family have had excellent visual acuity. Polar cataracts and corneal changes did not appear to affect visual function early in life or induce significant amblyopia. Significant cataracts have supervened in three of our patients (in two at a young age) and in two of Dohlman's older patients, all of which required extraction. Jaafar and Robb[2] stressed the possibility of progression of anterior polar cataracts to significant cataracts requiring extraction and advised close follow-up of children with anterior polar cataracts.

Corneal edema developed in the proband of the present family only several years after cataract surgery. Thus, corneal abnormalities in this disease may only lead to significant visual impairment when additional surgical trauma has been incurred.

Familial occurrence of Fuchs' dystrophy or cornea guttata is well known, and the condition is probably inherited in an autosomal dominant fashion.[3-7] Anterior polar cataracts, when familial, are also inherited in an autosomal dominant fashion. Anterior polar cataracts may occur in association with other ocular abnormalities such as aniridia or Peters' anomaly. We believe that more families with cornea guttata and anterior polar cataracts are potentially identifiable if patients with either component of the syndrome are carefully examined for the other ocular abnormality.

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The Effect of Increased Intraocular Pressure on Visual Acuity and Corneal Curvature After Radial Keratotomy

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To detect the effect of increased intraocular pressure on visual acuity and corneal curvature after radial keratotomy, we measured these variables in the sitting and inverted positions in 18 patients who underwent radial keratotomy (Group 1) and compared their results with those from the unoperated on eyes of seven patients (Group 2). We also compared the results before and after inversion within each group. Intraocular pressure increased to approximately two times normal in each group. Significant improvement in visual acuity and reduction in central keratometry were noted only in Group 1. By multiple regression analysis, visual improvement correlated with the number of incisions but not the time since surgery. Our study provides evidence that increased intraocular pressure may account for transient changes in vision and corneal curvature after radial keratotomy.

INTRAOCULAR PRESSURE may be an important variable influencing both the success of radial keratotomy and the fluctuations of vision experienced postoperatively.[1,2] Many surgeons take intraocular pressure into account when planning the optical zone size and the number and the length of the corneal incisions.[3] Intraocular pressure rises with changes in body position.[4,5] Herein we used changes in body position to study the effect of increased intraocular pressure on corneal curvature and visual acuity in patients who have undergone radial keratotomy.

Accepted for publication May 5, 1989.
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Subjects and Methods

Eighteen healthy patients who underwent radial keratotomy were included in one of two groups. Group 1 (radial keratotomy) consisted of one eye each of 18 patients who underwent either unilateral or bilateral radial keratotomy. For the 11 patients who underwent bilateral radial keratotomy, the selected eye was chosen randomly. Eight eyes had four incisions, eight eyes had eight incisions, one eye had 12 incisions, and one eye had 16 incisions. Surgery was performed between one and 48 weeks before this study (mean, 16.9 weeks). The mean age was 36.3 years (range, 22 to 53 years). The preoperative refraction was -3.79 ± 1.50 diopters (mean ± S.D.). Group 2 (control) consisted of the unoperated on eye of the seven patients who underwent unilateral radial keratotomy. The average age of these control subjects was 39.7 years (range, 24 to 53 years) and their mean refraction was -3.59 ± 1.17 diopters.

A masked observer examined both eyes of each subject in a sitting position for intraocular pressure, uncorrected visual acuity, manifest refraction, and keratometry at the steep and flat medians. Intraocular pressure was measured with a calibrated pneumatonometer.

To increase intraocular pressure, the subject was positioned head down using gravity inversion boots. Intraocular pressure was measured one minute later. (Stabilization of intraocular pressure in this position takes 15 to 30 seconds.) Uncorrected visual acuity was measured with an upside down Snellen acuity chart and corneal curvature was measured with a keratotometer placed onto the floor with the chin rest removed after intraocular pressure stabiliza-

tion. Thereafter, the patient was returned to the upright sitting position and intraocular pressure was measured at one-minute intervals until it returned to baseline levels. Uncorrected visual acuity and keratometry readings were obtained at five-minute intervals until they, too, returned to baseline levels.

For data analysis, keratometry readings from the steep and flat axes were averaged. A two-tailed unpaired *t*-test was used to compare mean values between the two groups ($P < .05$ was considered significant). A two-tailed paired *t*-test was used to compare the values before and after inversion in each group ($P < .05$ was considered significant). Multiple regression was used to assess the correlation between changes in vision and curvature with the number of incisions, refraction, subject's age, and the time in weeks since surgery.

Results

The refraction after radial keratotomy was reduced to -1.08 ± 0.78 diopters (mean ± S.D.) in Group 1. Of the 18 eyes in Group 1, 11 (61%) had a refraction between -1.25 and $+0.50$ diopters. Only one eye (5.6%) was slightly overcorrected. There were no significant differences in age, sex, or preoperative refraction between the two groups.

The change in intraocular pressure after inversion was not different between the two groups: Group 1, 12.6 ± 2.5 mm Hg and Group 2, 13.7 ± 2.6 mm Hg ($P > .05$) (Tables 1 and 2). Statistically and clinically significant keratometric flattening and visual improvement with inverted positioning were noted in Group 1.

TABLE 1
SUMMARY OF CLINICAL DATA*

PATIENT NO., AGE (YRS)	EYE	TIME SINCE SURGERY (WKS)	NO. OF INCISIONS	KERATOMETRY (D) (FLAT/STEEP, AXIS) BEFORE INVERSION	AFTER INVERSION	SNELLEN VISUAL ACUITY BEFORE INVERSION	AFTER INVERSION	INTRAOCULAR PRESSURE (MM HG) BEFORE INVERSION	AFTER INVERSION	REFRACTION
1, 40	R.E.	6	4	40.00/40.00	39.00/39.25, 165	20/20	20/20	10	21	Plano +1.00 × 180
2, 35	L.E.	12	16	43.00/45.00, 95	42.50/44.25, 95	20/200	20/50	10	19	−2.50 +1.00 × 90
3, 53	R.E.	—	0	42.00/43.25, 100	42.25/43.25, 100	20/300	20/300	15	25	−4.75 +1.75 × 105
	L.E.	40	4	40.12/40.25, 180	40.25/40.50, 175	20/40	20/40	15	25	−1.00 +0.50 × 180
4, 41	R.E.	12	4	41.25/42.75, 90	40.00/41.50, 92	20/30	20/20	14	28	−1.50 +0.75 × 85
5, 40	R.E.	32	8	41.75/43.50, 90	41.25/42.25, 90	20/40	20/30	15	27	−1.50
	L.E.	—	0	44.50/45.00, 90	44.25/45.75, 90	20/400	20/400	15	25	−4.50
6, 29	R.E.	3	8	46.00/46.50, 180	44.50/45.00, 175	20/200	20/50	9	25	−2.00
7, 28	R.E.	16	8	42.00/43.75, 80	41.75/43.75, 82	20/40	20/30	12	24	−2.25 +0.50 × 90
8, 40	R.E.	32	8	43.50/43.75, 85	43.12/43.50, 90	20/30	20/30	12	24	−1.50 +0.50 × 180
9, 40	R.E.	—	0	45.25/46.00, 15	45.00/45.75, 15	20/300	20/300	10	17	−3.50 +1.25 × 15
	L.E.	16	8	41.50/42.75, 168	40.75/41.75, 168	20/25	20/20	10	17	−0.75 +1.00 × 165
10, 35	L.E.	48	8	40.00/40.50, 75	39.25/39.50, 75	20/30	20/20	10	25	−1.75 +3.00 × 75
11, 33	R.E.	—	0	43.75/44.00, 90	43.50/44.00, 90	20/400	20/400	16	27	−5.50 +0.75 × 90
	L.E.	4	12	41.50/43.25, 95	41.50/42.75, 90	20/200	20/50	16	25	−2.50 +1.00 × 95
12, 44	R.E.	3	4	41.75/42.50, 90	40.25/41.75, 90	20/40	20/40	14	25	−1.25 +0.75 × 90
	L.E.	—	0	44.00/45.12, 80	43.75/45.00, 80	20/300	20/300	15	25	−4.25 +0.75 × 80
13, 43	L.E.	4	4	44.12/44.87, 90	43.87/44.50, 90	20/40	20/20	18	33	−0.75
14, 41	R.E.	20	4	39.50/39.50, 90	38.50/38.75, 85	20/30	20/25	12	29	−1.75 +1.00 × 90
15, 40	R.E.	12	8	41.50/43.00, 90	41.00/43.00, 90	20/30	20/20	15	28	−1.00 +1.50 × 90
	L.E.	—	0	43.50/44.50, 90	43.50/44.50, 90	20/70	20/70	15	28	−2.25
16, 21	L.E.	1	4	39.75/41.00, 100	39.25/40.75, 85	20/25	20/20	11	27	−0.25
17, 28	R.E.	12	4	40.50/41.25, 85	40.25/41.00, 85	20/25	20/20	10	25	−0.50
	L.E.	—	0	42.50/43.25, 95	42.50/43.25, 95	20/70	20/70	10	27	−2.50
18, 22	L.E.	32	8	44.50/44.87, 90	43.75/44.25, 90	NA	NA	13	30	−2.00

*NA, not available.

TABLE 2
COMPARISON OF BEFORE AND AFTER INVERSION DATA

GROUP	INTRAOCULAR PRESSURE (MM HG)			MEAN VISUAL ACUITY (± LINES OF SNELLEN ACUITY)			MEAN KERATOMETRY (D)		
	BEFORE INVERSION	AFTER INVERSION	P VALUE*	BEFORE INVERSION	AFTER INVERSION	P VALUE*	BEFORE INVERSION	AFTER INVERSION	P VALUE*
Group 1 (Radial keratotomy)	12.6 ± 2.5	25.5 ± 3.9	0.0001	20/40 ± 2.8	20/25 ± 1.5	0.001	42.3 ± 1.8	41.6 ± 1.8	0.0001
Group 2 (Control)	13.7 ± 2.6	24.9 ± 3.7	0.0001	20/100 ± 2.2	20/100 ± 2.2	>.05‡	44.4 ± 1.0	44.3 ± 0.9	>.05
P value†	>.05	>.05	—	0.01	0.001	—	0.01	0.001	—

*Two-tailed, paired *t*-test.
†Two-tailed, unpaired *t*-test.
‡Nonparametric sign test.

Visual acuity did not improve beyond the 20/20 level. After repositioning the patient to the upright posture, visual acuity and keratometry returned to baseline after five to 45 minutes.

Multiple regression analysis showed that visual improvement significantly correlated with a greater number of incisions ($P < .01$) and postoperative refraction ($P < .025$), but not with the length of the postoperative period ($P < .10$) or age ($P > .05$). Corneal flattening was not found to relate statistically to the number of incisions, the length of the postoperative period, age, or postoperative refraction.

Discussion

The correlation of improved visual acuity with increased intraocular pressure after radial keratotomy in humans has not been well documented[6,7]; however, overcorrected patients are often prescribed pressure-lowering medications. The effect of intraocular pressure on corneal curvature has been examined in one patient,[8] as well as experimentally in rabbits[8] and primates.[9] In rabbits, increasing intraocular pressure to 80 mm Hg resulted in a significant flattening of the cornea for up to four months after surgery. Statistically significant differences in flattening with time were noted only for the higher intraocular pressure intervals (40 to 60 and 60 to 80 mm Hg).[9] Increasing intraocular pressure in the physiologic range (10 to 20 mm Hg) did not significantly alter central keratometry in primates.[10]

In our study, postural inversion served as a reliable and reproducible method of increasing intraocular pressure twofold. In those eyes that had undergone radial keratotomy, the increase in intraocular pressure resulted in flattening of the cornea and an improvement of visual acuity. The cornea, behaving like a distensible membrane, obeyed Poisson's equation[11]:

$$-\nabla^2 Z = \frac{P}{T},$$

where T is the corneal surface tension, P is the pressure, $-\nabla^2$ is the Laplacian operator, and Z is the displacement of the corneal surface. With $-\nabla^2 Z$ proportional to the inverse of the radius of curvature,[12] Poisson's equation can be simplified to:

$$P \propto \frac{T}{R},$$

with R being the radius of curvature. In the normal cornea, when the intraocular pressure is raised the surface tension is also increased, thereby keeping the radius of curvature constant. However, the surface tension is lowered at the incision sites in the cornea after radial keratotomy and when the intraocular pressure is increased, the radius of curvature must also decrease. As the intraocular pressure increases, the shearing forces of the corneal collagen fibrils are overcome so the cornea is stretched and, later, is ruptured at the wounds. Au and Rowsey[13] also applied a similar equation in their "bending moment modeling" formula to predict corneal changes after refractive surgery.

After reinversion, intraocular pressure returned to baseline levels within one minute.

However, for visual acuity and corneal curvature, a lag time of five to 45 minutes was found, indicating altered corneal elasticity.

Visual improvement correlated significantly with a greater number of incisions and a reduction of the refractive error but not with keratometric flattening. The latter may be explained by a lack of one-to-one correlation of changes in keratometry and visual acuity after radial keratotomy.[14-16] However, visual improvement, keratometric flattening, and reduced refractive error did not correlate with a longer postoperative period. The lack of correlation may be explained by the wounds not being well-cemented together even years after surgery.[17-19]

Radial keratotomy modifies the corneal response to changes of intraocular pressure. Increased intraocular pressure may have exerted its central effect by steepening of the weakened and scarred peripheral cornea[8] or by gaping of the incisions.[20] Alteration of corneal elasticity by radial keratotomy may have accounted for the delayed recovery of baseline shape after return of intraocular pressure to normal levels. Our study provides evidence that transient changes in vision may occur in individuals after radial keratotomy.

ACKNOWLEDGMENT

Leonard Haff, Ph.D., performed the statistical analysis.

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Test-Retest Variability in Glaucomatous Visual Fields

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We measured test-retest variations in computerized visual fields from glaucomatous eyes. Fifty-one patients were tested four times within a four-week period; the severity of disease varied from incipient to advanced. We determined the dependence of threshold variability on defect depth and test point location. In areas of the visual field initially found to have moderate loss of sensitivity, variation in follow-up measurements ranged from normal sensitivity to absolute defect, with little dependence on distance from fixation. Conversely, large changes were considerably more unusual in locations initially showing normal or near-normal sensitivities, and variability was lowest in the most central portion of the field. Our findings suggest that differentiation between true progression and random variation will be facilitated if these factors are taken into account, as well as if comparisons are based on more than two tests. The complex nature of intertest variation in glaucoma makes it natural to approach this problem with the help of computer-assisted analyses.

COMPUTERIZED PERIMETRY, and particularly automated static threshold perimetry, is becoming the standard method for visual field testing in glaucoma management. This type of examination has been shown to be a sensitive method for detection of early glaucomatous field loss. Many investigations have shown, however, that intra-individual variability of the differential light threshold is considerable, and that this variability is particularly large in glaucomatous fields.[1-10] This lack of stability makes the differentiation between nonsignificant random variation and true progression in glaucoma patients difficult, and is a constant problem in the treatment of these patients. Quantification and better understanding of intertest variability in glaucomatous fields could constitute a first step toward a solution of this problem.

See also p. 189.

We undertook this study to measure intertest variation of the differential light threshold in patients with glaucoma of varying severity. We wanted to quantify pointwise fluctuations of the differential light sensitivity, and particularly to see whether variability is influenced by the degree of abnormality and by test point location.

Material and Methods

Subjects—We studied 51 eyes from 51 patients with glaucoma of varying severity. The patients ranged in age from 33 to 82 years (average, 66 years). The patients were selected in such a way as to represent all stages of glaucoma (Fig. 1). Most of the eyes had documented visual field loss, ranging from subtle to advanced. The investigation was not limited, however, to patients with known field defects; we also included some eyes where results of earlier field tests had been normal or questionably abnormal, but where optic nerve findings and intraocular pressure clearly indicated that the eye was glaucomatous. In all such cases, the fellow eye showed definite glaucoma with nondisputable visual field defects. Eyes with dense cataracts were excluded, but some with early lens opacities and a visual acuity of 20/30 or better were included. All patients had previous experience with computerized threshold perimetry, and most of them had undergone many examinations of this type.

Accepted for publication April 24, 1989.
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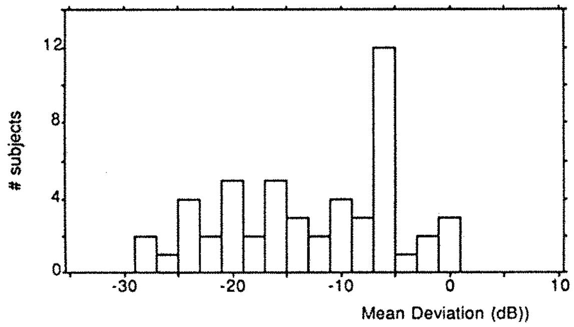

Fig. 1 (Heijl, Lindgren, and Lindgren). Distribution of mean deviation (MD) values in studied eyes. Mean deviation is a weighted average deviation of measured thresholds from age-corrected normal reference values.[13] Studied eyes covered the whole spectrum of disease from nearly normal (mean deviation ≈ 0) to severe field loss.

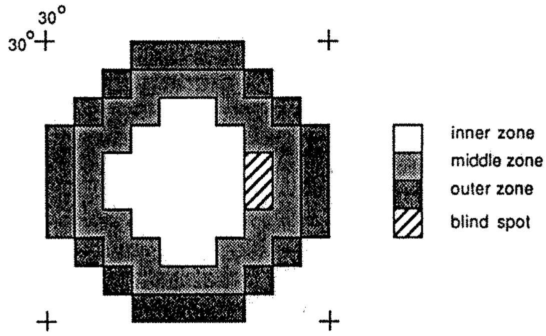

Fig. 2 (Heijl, Lindgren, and Lindgren). Pattern of 76 test points was divided into three zones for analysis of influence of eccentricity on intertest threshold variation.

Visual field testing—Visual fields were tested with automated threshold-measuring perimetry using the 30-2 program of the Humphrey perimeter.[11,12] The instrument was always used in the full threshold mode. Refractive correction appropriate for age and testing distance was provided. To test over a period of time that was small relative to times typically required for documentation of progression of field loss, one eye of each patient was tested once each week for four weeks. All patients continued their usual drug therapy during the study.

Data analysis—We calculated the difference between the measured threshold value and the age-corrected normal threshold value from the Statpac analysis program[13] at each point of every tested field, except at two points in the blind spot area. This difference is called the total deviation at that point. All tested locations from the first field test of each patient were then ranked according to this deviation, and divided into groups in steps of 2 dB (0.2 log units). In this way groups of points were created, where points within groups showed similar deviation from normal at the first examination. Our data fell into 22 such groups, with threshold deviations ranging from +8 to −34 dB.

In each group of first-time threshold deviations we calculated the percentiles of the measured threshold at the following test. We thus determined the frequency with which a given amount of change occurred from one test to the next as a function of the severity of the local field defects measured at the first test. Similar calculations were made for the second vs the third and third vs fourth tests. Loss-stratified histograms were then obtained by pooling the results between first and second, second and third, and third and fourth tests. Finally, prediction limits were computed in each of the 22 groups at the 2.5, 5, 50, 95, and 97.5 percentiles.

The effect of point location was studied by dividing the point pattern into three zones of increasing eccentricity (Fig.2) and again calculating prediction limits in the same way as described above.

In glaucoma, there is a considerable covariation of pointwise deviations with those of neighboring points; that is, in considering the results of a single test, if one point is abnormal there is an increased likelihood that nearby points are also abnormal. Nasal steps and arcuate defects illustrate this covariation. We hypothesized that a similar covariation is found from test to test. For instance, if in a follow-up testing of a patient with established field loss, one point showed progression, then there should be an increased probability that nearby points have also deteriorated. For each point in each measured field we calculated the difference between the measured threshold value and the average threshold value of the four fields from the same eye. Correlation coefficients were then computed for all such deviations as a function of interpoint distance.[14]

Averaging results from several tests should increase the precision of threshold estimates and yield a better baseline for future comparisons. We studied the effect of such averaging by comparing the threshold prediction limits when the defect depth of individual points was based on the results of one, two, or three field tests, respectively, and also when intertest changes were judged by comparing the results of two initial with two later field charts. In these

cases the deviation of sensitivity from the age-corrected normal value at a point was defined as the average of the deviations at two or three consecutive tests, respectively.

Results

Intertest variation differed considerably between test points with normal compared to abnormal differential light thresholds (Fig. 3). Intertest variability was generally quite large and increased considerably with defect depth. Points with an initially measured sensitivity equal to the age-corrected normal threshold level stayed within +3 to −7 dB from the normal value 90% of the time. But, as initial defect depth increased to −6 dB, the 90% prediction interval increased to cover the range from −1 dB to −16 dB, and was even larger in areas with greater defect depth. Thus, in points with initial total deviations of approximately −8 to −18 dB, the 95% prediction interval encompassed almost the full spectrum from normal sensitivities to absolute defects. In points with even lower sensitivity, 18 dB or more below the age-corrected normal threshold value, intertest threshold variability decreased slightly, although still remaining large. We examined four categories of defect depth (0 to −6 dB, −6 to −12 dB, −12 to −18 dB, and −18 to −24 dB), and found their intertest threshold variabilities to be significantly different from each other ($P < .01$, F-test; number of degrees of freedom reduced due to dependence).

Intertest variability was more highly correlated between closely neighboring test points than it was between widely separated points (Table).

As anticipated, intertest variability decreased when comparisons were based on the averages of several tests. Figure 4 shows changes when averages from two initial measurements were compared with averages of two follow-up threshold tests. Percentiles were narrower over the whole range of sensitivities as compared with those shown in Figure 3.

Intertest threshold variation increased with eccentricity but only in points where initial threshold deviations departed from the age normal by less than 10 dB (Fig. 5). In such points, threshold variability was significantly larger in the outer zone than in the inner zone ($P < .01$; F-test). These relationships between the variability of points at different locations also remained similar when averages of tests were compared.

Discussion

The results of the present study confirm and quantify earlier observations that glaucomatous visual field results are subject to considerable intertest variation.[1,2,3,8,10] Our results further indicate that pointwise intertest fluctuations are related to the status of the point, in general increasing with progressing abnormality. In individual points, even large variations may be encountered in the absence of any true

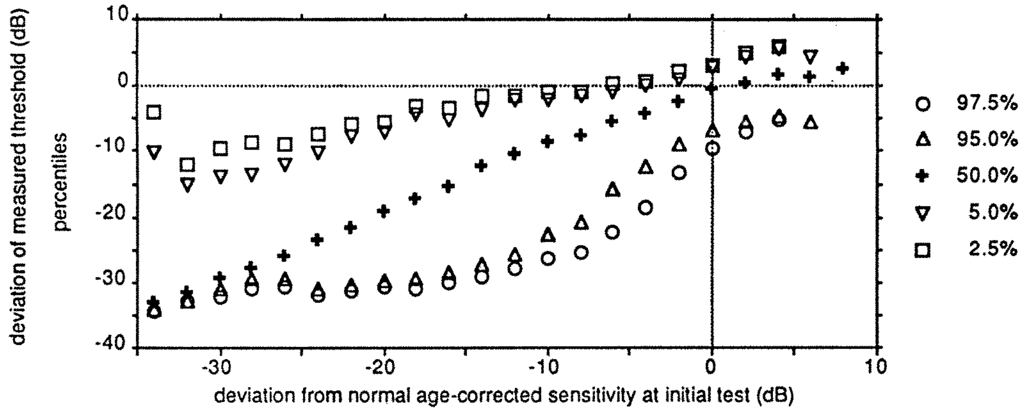

Fig. 3 (Heijl, Lindgren, and Lindgren). Pointwise threshold change from one test to the next as a function of deviation from normal at preceding test. Intertest variation at points initially having normal or nearly normal sensitivity was considerably smaller than it was at locations initially showing moderately diminished sensitivity. In points initially found to have moderate loss, random variation covered the whole range from normal sensitivities to absolute defects.

TABLE
CORRELATIONS OF THRESHOLD VARIATION AS A FUNCTION OF DISTANCE BETWEEN TEST POINTS

	APPROXIMATE INTERPOINT DISTANCE (DEG)							
	6	8.5	13	17	24	33	41	52
Mean correlation	0.200	0.161	0.096	0.071	0.056	0.046	0.054	0.051

progression or improvement of the patient's disease. A reduction of the measured threshold by, for example, 10 dB may fall entirely within the predicted variation, if occurring in a point where sensitivity is initially reduced by 10 to 20 dB. In normal areas or in areas with only shallow field loss, variability also depended on point location. This is in concordance with previous studies, which have shown that intertest threshold variability in normal subjects strongly depends on eccentricity.[5,6,9]

From a practical point of view one must, therefore, be cautious before interpreting localized measured threshold differences between two tests as signs of progression or regression of the glaucomatous disease process. In moderately deep field defects the expected pointwise random variation covers the whole spectrum from normal sensitivity to an absolute defect. This means that in such areas no conclusions may be drawn from threshold variations at a single point when only two tests have been done, regardless of the magnitude of these changes. In points with normal or only slightly reduced sensitivity, on the other hand, large intertest variations are unusual. Successful differentiation of true localized progressive glaucomatous field loss from random intertest variation is therefore unlikely unless defect depth and point location are both taken into account. The chances of identifying small deteriorating areas will increase considerably if results from more than two tests are available.

Our numerical results are similar to those of Werner and coworkers.[10] However, while recognizing that fluctuations tend to increase in more severely damaged fields, they did not separate variability according to pointwise severity of field loss. They concluded that in order to detect progressive glaucomatous visual field damage, the change in any area of the visual field would have to be greater than 6.4 dB per test location. We cannot agree with this conclusion. As stated previously, pointwise threshold changes of this magnitude may be either significant or the effect of random variation depending on the severity of field loss and the location of the point.

Interpretation of intertest differences of glaucomatous fields may thus be facilitated if defect depth and point location are taken into account. In a clinical situation, two rules of thumb may be useful: (1) points with normal and near-normal sensitivity should be expected to show less random variation than points in deeper field defects and (2) variation in shallow defects increases with eccentricity. The "normal" threshold variation in glaucoma is, however, complex and its detail and magnitude difficult or impossible to memorize. A computer, for example, that of the perimeter, can easily store any data on this expected variability, its dependence on defect depth, and on point location, as well as the limits for reaching various levels of statistical significance. The

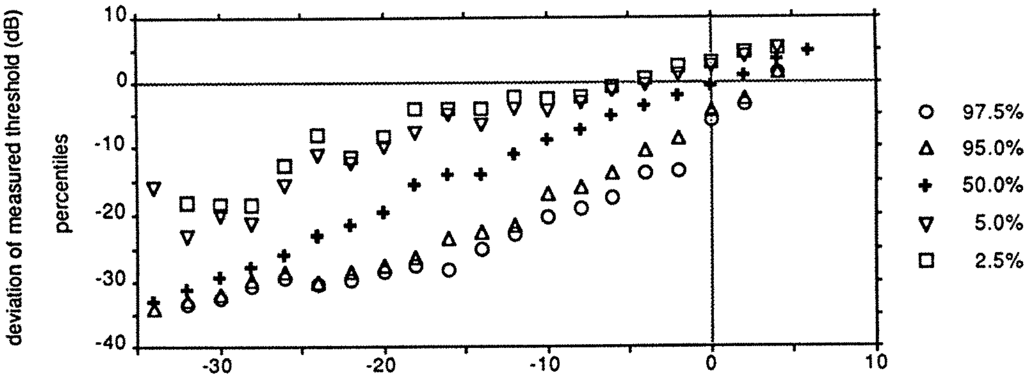

Fig. 4 (Heijl, Lindgren, and Lindgren). Pointwise threshold change as in Figure 3, except using average of tests 1 and 2 to establish baseline and average of tests 3 and 4 as follow-up. Variability was naturally lower when more tests were used, considerably facilitating ability to detect true changes.

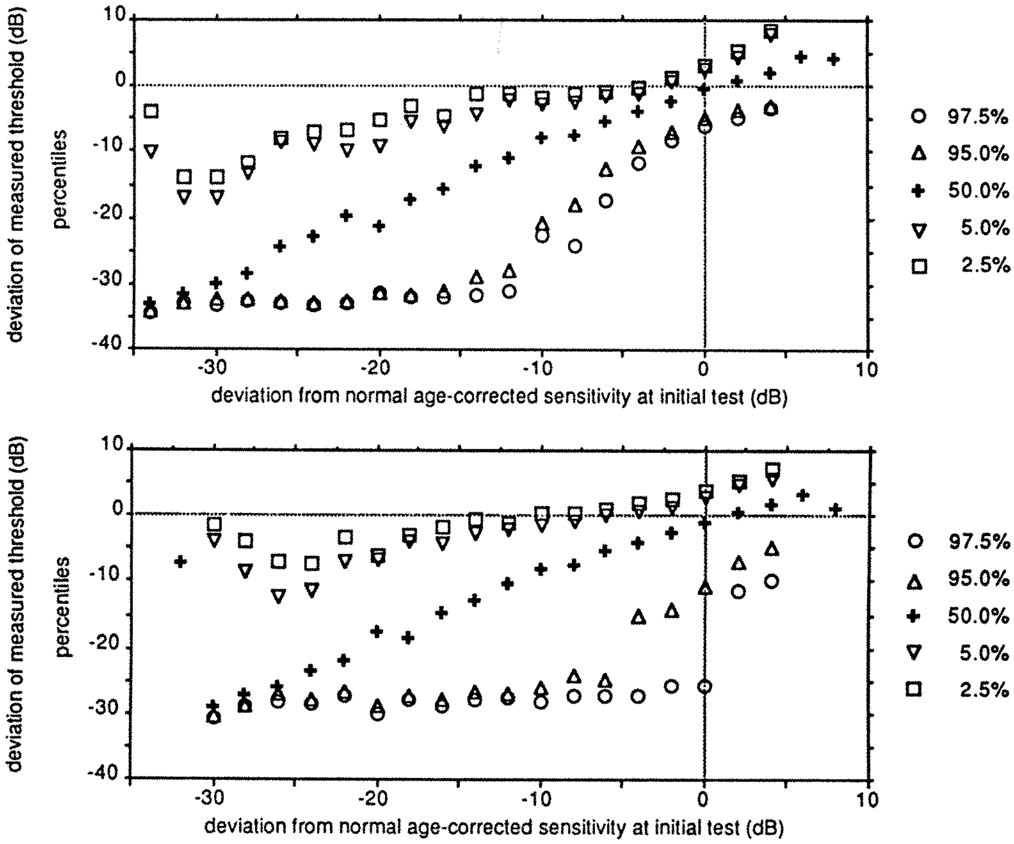

Fig. 5 (Heijl, Lindgren, and Lindgren). In points with normal or slightly reduced sensitivity, variability was smaller centrally than more peripherally. Top, Variability in inner zone; bottom, variability in peripheral zone (see Fig. 2). No eccentricity dependence was seen in points with moderate to marked sensitivity loss.

computer could then calculate and graphically display significances of measured intertest differences of pointwise threshold values. Such an approach could be clinically useful in two ways: (1) it could facilitate the detection of progression in glaucoma and (2) it could help us discount apparent but nonsignificant deterioration, thus encouraging further evaluation in questionable cases.

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Ophthalmic miniature

Grandmother's Eye-Wash—Take three fresh eggs and break them into one quart of clear, cold rain-water; stir until thoroughly mixed; bring to a boil on a slow fire, stirring often; then add half an ounce of sulphate of zinc (white vitriol); continue the boiling for two minutes, then set it off the fire. Take the curd that settles at the bottom of this and apply to the eye at night with a bandage. It will speedily draw out all fever and soreness. Strain the liquid through a cloth and use for bathing the eyes occasionally. This is the best eye-water ever made for man or beast. I have used it for twenty years without knowing it to fail.

Hugo Zieman and Mrs. F. L. Gillette, *The White House Cook Book*
New York, The Saalfield Publishing Company, 1907, p. 518

Complications After Surgery for Congenital and Infantile Cataracts

Ronald V. Keech, M.D., Andrea Cibis Tongue, M.D., and William E. Scott, M.D.

We reviewed the records of 78 patients who underwent 128 surgical procedures for congenital or infantile cataracts before age 30 months for the type and frequency of postoperative complications. The surgeries included 92 limbal lensectomies and anterior vitrectomies, 13 pars plicata lensectomies, 20 aspirations, and three additional procedures. Complications developed after 21 of the 105 lensectomy and anterior vitrectomy procedures. Ten eyes (10%) required additional surgery for a secondary membrane, 12 eyes (11%) developed glaucoma, and one (1%) developed a retinal detachment. Patients who underwent surgery by 8 weeks of age had a significantly greater number of complications ($P < .025$). Patients undergoing cataract surgery early in life should be routinely examined for possible postoperative glaucoma. The best method for reducing secondary membrane formation and some types of glaucoma appears to be an extensive removal of the lens cortex, posterior capsule, and anterior vitreous.

THE CURRENT MOST COMMON cataract procedure in young children is the removal of the lens and anterior vitreous with automated vitrectomy instruments.[1] Along with a more complete removal of the lens and vitreous, there is an apparent reduction in the complications associated with this approach. Peyman and associates[2] reported three complications in 32 automated lensectomies and vitrectomies using a pars plicata incision. Chrousos, Parks, and O'Neil[3] found two cases each (5%) of glaucoma and retinal detachment, and four cases (5%) of secondary membrane formation with a lensectomy and anterior vitrectomy in 88 eyes. Taylor[4] noted no complications in 23 eyes operated on using a similar surgical procedure.

To evaluate the incidence and type of complications further, we reviewed all cases of congenital and infantile cataracts that were seen at the University of Iowa Pediatric Ophthalmology Service from 1974 to 1986 and in a private pediatric ophthalmology practice from 1979 to 1986.

Accepted for publication May 15, 1989.

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Material and Methods

We reviewed the records of all patients who underwent cataract surgery before age 30 months. Patients with persistent hyperplasia of the primary vitreous were excluded. Several surgeons were involved in these cases, with most procedures being performed by pediatric ophthalmologists. The surgical technique varied over the time period studied. The earlier procedures were generally one or two needling aspiration techniques without a posterior capsulotomy. The more recent surgeries consisted of a lensectomy, posterior capsulectomy, and anterior vitrectomy with automated vitrectomy instruments introduced through the pars plicata or corneoscleral limbus. The postoperative follow-up period was to the latest examination for each patient. Visual acuities were recorded using Snellen letters, illiterate E's, Allen pictures, or fixation preference, depending on the ability of the child.

Results

A total of 128 cataract procedures were performed on 78 patients (Table 1). There were 92 automated lensectomies and anterior vitrectomies through a limbal incision and 13 automat-

TABLE 1
SURGICAL PROCEDURE AND POSTOPERATIVE FOLLOW-UP

SURGICAL PROCEDURE	NO.	LENGTH OF FOLLOW-UP (MOS) ≤12	>12-60	>60
Aspiration	20	3	9	8
Limbal lensectomy/ vitrectomy	92	11	59	22
Pars plicata lensectomy/ vitrectomy	13	4	7	2
Other	3	0	2	1
Total	128	18	77	33

*Mean length of follow-up, 44.8 months.

ed lensectomies and anterior vitrectomies through a pars plicata incision. Twenty cataracts underwent needling and aspiration without posterior capsulotomy. Three additional eyes underwent lens aspiration with a discission of the posterior capsule.

The postoperative follow-up period ranged from one to 158 months (mean, 44.8 months). The aspiration group had a mean follow-up of 60 months compared with 41 months for the combined limbal and pars plicata lensectomy and vitrectomy group.

Ocular complications occurred in 38 eyes of 30 patients during their postoperative course (Tables 2 and 3). The most frequent complication was the formation of secondary membrane or opacification of the posterior capsule obscuring the visual axis. This occurred in 15 of 20 eyes (75%) after lens aspiration with an intact posterior capsule. Opacification of the visual axis also occurred in ten of 92 eyes (11%) after automated lensectomy, posterior capsulectomy, and anterior vitrectomy through the corneoscleral limbus. No secondary membranes occurred after lensectomy/vitrectomy through the pars plicata, although there were only 13 such cases. The average time between cataract surgery and the obscuration of the visual axis was 5.3 months (range, one to 14 months) for the aspiration technique and 11.6 months (range, two months to four years) for the lensectomy and vitrectomy group.

Glaucoma was the second most common complication, occurring in 16 eyes of 12 patients. One patient developed acute pupillary block in one eye after an aspiration procedure. Five eyes developed chronic closed-angle glaucoma, which was not discovered until several years after the cataract surgery. All of these eyes demonstrated peripheral anterior synechiae and required treatment with medication or surgery.

Four patients (six eyes) had anomalies of the anterior chamber angle similar to congenital glaucoma. Each eye had a flat iris plane with no angle recess and a poorly defined scleral spur and ciliary body. Prominent iris processes and peripheral iris hypoplasia were present in some cases. One of these patients (one eye) had Lowe's syndrome, with increased intraocular pressure noted before surgery. One additional patient (one eye) with bilateral cataracts had the more extensive cataract removed at 6 weeks of age, with uncontrollable glaucoma noted two months after surgery. Gonioscopy repeated over several months showed angle anomalies in both eyes, but more extensive changes in the aphakic eye. Retained lens cortex was also noted in the anterior chamber of the aphakic eye. The two remaining patients (four eyes) had a family history of infantile cataracts and early onset glaucoma. Both of these patients, as well as five of their family members, had anomalous angles.

Glaucoma associated with open angles oc-

TABLE 2
COMPLICATIONS AFTER SURGERY FOR CONGENITAL AND INFANTILE CATARACTS

COMPLICATION	ASPIRATION (N = 17)	LIMBAL LENSECTOMY AND ANTERIOR VITRECTOMY (N = 19)	PARS PLICATA LENSECTOMY AND ANTERIOR VITRECTOMY (N = 2)	TOTAL (N = 38)
Secondary membrane	15	10	0	25
Chronic closed-angle glaucoma	2	3	0	5
Pupillary block glaucoma	1	0	0	1
Open-angle glaucoma	1	2	1	4
Anomalous angle	0	5	1	6
Retinal detachment	1	1	0	2

TABLE 3
PATIENTS WITH COMPLICATIONS AFTER SURGERY*

PATIENT NO.	AGE AT SURGERY	EYE	PROCEDURE	COMPLICATION OR SECONDARY PROCEDURE AFTER CATARACT SURGERY	AGE AT LAST EXAM (YEARS)	VISUAL ACUITY AT LAST EXAM
1	9 mos	L	ASP	Discission at 14 mos, chronic closed-angle glaucoma at 12 yrs	13 2/12	CF at 4'
2	24 mos	R	ASP	Discission at 3 and 7 mos	12 6/12	CSUM
3	4 mos	L	ASP	Discission at 10 mos	2 3/12	UCUSUM
4	5 mos	R	ASP	Discission at 2 mos, open-angle glaucoma at 6 yrs	12 3/12	20/80
	8 mos	L	ASP	Membranectomy at 6 wks, retinal detachment at 4 mos		20/400
5	10 mos	L	ASP	Discission at 4 and 7 mos	10 2/12	20/200
6	3 mos	R	ASP	Membranectomy at 1 mo	3 11/12	20/200
	5 mos	L	ASP	Membranectomy at 7 mos		20/60
7	4 mos	R	ASP	Membranectomy at 6 mos	2 6/12	UCUSUM
	5 mos	L	ASP	Membranectomy at 10 mos		UCUSUM
8	2 mos	L	ASP	Chronic closed-angle glaucoma at 4 yrs	4 9/12	20/60+2
9	30 mos	L	ASP	Membranectomy at 2 mos	2 7/12	CSUM
10	6 wks	L	ASP	Membranectomy at 7 mos	4 7/12	20/50
11	5 mos	R	ASP	Membranectomy at 2 wks	5	20/70
12	16 mos	L	ASP	Membranectomy at 1 yr	5 8/12	20/40
13	5 mos	L	ASP	Pupillary block glaucoma at 1 wk	11/12	CSUM
14	7 mos	L	ASP	Membranectomy at 6 wks	9/12	CUSUM
15	3 wks	L	LLV	Membranectomy at 2 yrs	6 2/12	20/40
16	2 mos	L	LLV	YAG membranectomy at 4 yrs	4 2/12	20/60
17	6 wks	L	LLV	Membranectomy at 5 mos	2 5/12	20/200
18	3 wks	R	LLV	Secondary membrane at 9 mos	2 2/12	UCUSUM
19	10 days	R	LLV	Membranectomy at 2 mos	11/12	CUSUM
20	7 mos	R	LLV	Secondary membrane at 7 mos	7/12	CSUM
21	1 mo	L	LLV	Secondary membrane at 7 mos	1 10/12	CSUM
22	1 mo	R	LLV	Membranectomy at 2 mos	1 5/12	CSUM
23	2 wks	R	LLV	Anomalous angle at 2 wks, membranectomy at 5 mos	2 9/12	20/60
	4 wks	L	PPLV	Anomalous angle at 2 wks		20/60+
24	10 days	R	PPLV	Open-angle glaucoma with residual cortex at 3 mos	6 5/12	CF at 1 ft
25	3 mos	R	LLV	Closed-angle glaucoma at 6 yrs	6 8/12	20/100
	3 mos	L	LLV	Closed-angle glaucoma at 6 yrs		20/100
26	2 wks	R	LLV	Anomalous angle at 1 yr	3 2/12	UCUSUM
	3 wks	L	LLV	Anomalous angle at 1 yr		CSUM
27	2 wks	R	LLV	Open-angle glaucoma at 3 mos	4 7/12	20/70
	4 wks	L	LLV	Open-angle glaucoma at 3 mos		20/60
28	6 wks	L	LLV	Anomalous angle with residual cortex at 3 mos	1 7/12	UCUSUM
29	2 mos	R	LLV	Anomalous angle at 3 mos	2	CSUM
30	4 days	R	LLV	Vitreous hemorrhage and retinal detachment at 6 yrs	6 4/12	NLP
	9 days	L	LLV	Membranectomy at 7 mos, closed-angle glaucoma at 3 yrs		20/300

*ASP, aspiration; LLV, limbal lensectomy and vitrectomy; PPLV, pars plicata lensectomy and vitrectomy; CF, counting fingers; NLP, no light perception; CSM, central, steady, maintained; CSUM, central, steady, unmaintained; UCUSUM, uncentral, unsteady, unmaintained.

curred in one eye of the aspiration group and three eyes of the lensectomy and vitrectomy group. In one of these patients (one eye) congenital rubella was suspected and the other patient (two eyes) had greater than normal postoperative inflammation with retained lens material.

Two eyes sustained retinal detachments during the postoperative follow-up period. One detachment occurred four months after the primary lensectomy by an aspiration technique and two months after membranectomy with an automated vitrectomy instrument. The second detachment occurred six years after lensectomy and anterior vitrectomy through the corneoscleral limbus and two years after a pars plana vitrectomy for a spontaneous vitreous hemorrhage.

A comparison of the age at surgery was made between the complicated and uncomplicated cases to assess the effect of early intervention (Table 4). Only three patients had an uncomplicated course in the aspiration group and no statistical comparison was possible. In the lensectomy and vitrectomy group, 18 of 64 patients (28%) undergoing surgery at 2 months of age or younger experienced complications compared with four of the 41 patients (10%) who were older than 2 months at the time of surgery ($P < .025$).

The patients with systemic and additional ocular abnormalities were compared in the complicated and uncomplicated groups (Table 5). Other ocular abnormalities found in this series included microphthalmos, iris colobomas, ectopic pupil, corneal opacities, and optic nerve hypoplasia. Nine of 38 eyes (24%) in the complicated group had other ocular abnormalities compared with 15 of 90 eyes (17%) in the uncomplicated group ($P > .10$). Systemic abnormalities found in this series included Lowe's syndrome, congenital rubella syndrome, Down's syndrome, Cockayne's syndrome, Schwartz-Jampel syndrome, Hallermann-Streiff syndrome, craniosynostosis, congenital deafness, seizure disorder, absent corpus callosum, and developmental delay. Eight of 30 patients (27%) in the complicated group had systemic abnormalities compared with only nine of 98 (9%) in the uncomplicated group ($P < .025$).

TABLE 4
COMPARISON OF AGE AT SURGERY AND RATE OF COMPLICATIONS

SURGICAL PROCEDURE	AGE AT SURGERY ≤2 MOS	>2–12 MOS	>12 MOS
Aspiration			
Eyes	2	15	3
Complications	2	12	3
Limbal lensectomy/ vitrectomy			
Eyes	53	29	10
Complications	16	3	1
Pars plicata lensectomy/ vitrectomy			
Eyes	11	2	0
Complications	2	0	0

TABLE 5
ASSOCIATED OCULAR AND SYSTEMIC ABNORMALITIES

POSTOPERATIVE COURSE	OCULAR ABNORMALITIES*	SYSTEMIC ABNORMALITIES†
Uncomplicated	17	9
Complicated	24	27

*% of eyes with ocular abnormalities.
†% of patients with systemic abnormalities.

Discussion

The complication rate after congenital cataract surgery has markedly decreased with the advent of automated lensectomy/vitrectomy techniques. Three recent studies[2-4] using this technique on a combined total of 143 eyes had an average complication rate of 8% compared with a 27% average complication rate for 1,416 surgical cases using older techniques in eight combined studies.[5-12]

In our series, we found a higher rate of complications than previously reported using lensectomy/vitrectomy techniques (Table 6). Of 105 eyes having undergone this procedure, 21 (20%) developed complications. Ten eyes required additional surgery because of obscuration of the visual axis from a secondary membrane, 12 eyes developed glaucoma, and one eye sustained a retinal detachment.

A difference among these studies that may affect the frequency of complications is the length of follow-up. The longer the postoperative period of evaluation, the more likely a higher complication rate. In our series, 105

TABLE 6
PEDIATRIC CATARACT SURGERY BY LENSECTOMY AND VITRECTOMY

STUDY	NO.	AGE AT SURGERY MEAN (RANGE)	MEAN FOLLOW-UP (MOS)	COMPLICATIONS (%)
Chrousos, Parks,	34	≤ 20 yrs	41	21
and O'Neill[3]	54	≤ 20 yrs	24	2
Peyman and associates[2]	32	5 yrs (1 mo–16 yrs)	28	9
Taylor[4]	23	17.4 wks (≤ 18 mos)	≥18	0
Present study	105	18 wks (1 wk–30 mos)	41	20

patients were followed up an average of 41 months after a lensectomy/vitrectomy procedure. This is longer than in most comparable studies.

Probably the most important factor contributing to the high complication rate is the patient's age at the time of surgery. We found a significant increase in the number of complications in patients operated on by 2 months of age as compared with children operated on after that age. This may be the result of technical difficulties associated with surgery on a neonate. Another factor may be the marked inflammation and scarring that often occurs after surgery in an immature eye. Any desire to delay surgery and possibly reduce the complication rate, however, must be balanced against the need to decrease the period of visual deprivation.[13,14]

All patients in our series were operated on by 30 months of age, with an average age at surgery of 18 weeks. Two other studies[2,3] using similar techniques included much older patients. In contrast, Taylor[4] reported no complications in 23 eyes operated on at an average age of 17.4 weeks. The number of patients operated on by 2 months of age in his series was not given.

Glaucoma after cataract surgery in young children is common and can result from a variety of mechanisms.[15-18] Anterior chamber angle abnormalities unrelated to cataract surgery may predispose to the development of postoperative glaucoma. Other forms of glaucoma are related to the postoperative inflammation and healing response. Finally, it has not been established whether or not glaucoma associated with open angles in aphakic patients can be directly attributed to the cataract surgery. Open-angle glaucoma has been described in association with congenital cataracts without preexisting surgery. This study suggests that patients undergoing cataract surgery early in life should be routinely examined for possible postoperative glaucoma.

The most frequent complication in our series was opacification of the posterior capsule or secondary membrane formation. As would be expected, secondary membrane surgery was common with the aspiration technique since the posterior capsule was left intact. Secondary membranes also occurred in some eyes after automated lensectomy and anterior vitrectomy. Others have reported similar findings.[19] In a number of our cases, lens cortex was noted postoperatively or the capsular opening was small and minimal vitreous was removed. Some eyes, however, had large posterior capsulectomies. We currently recommend extensive removal of lens cortex, posterior capsule, and anterior vitreous. This surgery should be aided, when necessary, by the use of intraocular dilating solutions, iris sphincterotomies or iridectomies, and transcorneal or intraocular fiberoptic illumination.

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Ophthalmic miniature

Soldiers, who used to exhaust ingenuity to procure their discharge, discovered that straining their eyes to distinguish objects through concave glasses, would make them what they desired—too short-sighted for the service. If they marred their vision they recovered their liberty.

Spectacles
Quart. Rev. vol. 87, 1850

Ocular Surgery on Patients Receiving Long-Term Warfarin Therapy

Steven P. Gainey, M.D., Dennis M. Robertson, M.D., William Fay, M.D., and Duane Ilstrup, M.S.

We analyzed data of 50 patients receiving long-term warfarin sodium therapy who underwent ocular surgery between 1982 and 1986. The frequency of hemorrhagic and thrombotic complications was compared in patients in whom anticoagulants were continued, those in whom the anticoagulants were discontinued in the perioperative period, and a group of matched control patients. There were six perioperative hemorrhagic complications in the warfarin-treated group (12%) compared to none in the control group. This difference was significant ($P < .03$). However, no significant difference in hemorrhagic complications was seen between patients in whom warfarin sodium was continued and those in whom it was discontinued.

Long-term oral anticoagulant therapy with warfarin sodium is instituted for a variety of medical conditions including prosthetic heart valves, atrial fibrillation, ischemic heart disease, cerebrovascular disease, and venous thromboembolism.[1] In patients receiving long-term anticoagulant therapy who require surgery, there are three options for the perioperative management of anticoagulant therapy.[2,3] First, surgery can be postponed, particularly if anticoagulants are being used to treat a temporary medical problem and it is anticipated that they will be discontinued. Second, anticoagulant therapy can be discontinued in the perioperative period. Although ideal from the surgeon's standpoint, this approach leaves the patient without anticoagulant therapy for varying lengths of time during which there might be an increased risk of thrombotic complications. To shorten this period of thrombotic vulnerability, intravenous heparin can be used except in the immediate perioperative period. The effects of anticoagulant therapy can also be reversed with vitamin K or clotting factor replacement. However, high doses of vitamin K can make reinstitution of anticoagulation therapy difficult, and clotting factor replacement is generally used only in the presence of life-threatening hemorrhages because of the infectious potential entailed. The final option in the treatment of such patients is to proceed with surgery without discontinuing the anticoagulant therapy. This, however, may be associated with an increased risk of hemorrhagic complications. Unfortunately, no clear protocol exists on how to treat these patients.

We undertook this study to determine how patients receiving long-term warfarin therapy were cared for at our institution and to learn if there were any differences in the local and systemic complication rates that relate to differences in perioperative management of anticoagulant therapy.

Material and Methods

Patients receiving long-term anticoagulant therapy who underwent ophthalmic surgery between 1982 and 1986 were identified by crossmatching the computerized listings of patients undergoing ophthalmic operations to the listing of patients with an increased prothrombin time. To avoid possible multiprocedure bias, only the first ophthalmic procedure performed on a given patient was analyzed. A control patient was identified for each study patient by matching age, sex, procedure, and time of surgery within one month.

Accepted for publication April 12, 1989.

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Patient data recorded included age, reason for and duration of anticoagulant therapy, concurrent aspirin therapy, nonsteroidal or dipyridamole therapy, type of procedure, method of management of anticoagulant therapy, and preoperative prothrombin values. Complications were recorded both for hemorrhagic and thrombotic complications. Prothrombin times were performed according to the method of Quick[4] before surgery. Preoperative prothrombin times were obtained within 24 hours of surgery. The normal prothrombin time at our institution during the study period was 10.9 to 12.5 seconds inclusive.

Fisher's exact test was used to compare complication rates between groups of patients. Continuous variables such as preoperative prothrombin time were compared between groups with rank sum tests. $P < .05$ was considered statistically significant.

Results

Of 50 patients identified for our study, 20 were men and 30 were women. Mean (± S.D.) age was 77 ± 10 years (range, 33 to 90 years), with a mean duration of warfarin therapy of 6.0 ± 5.4 years (range, one to 22 years). Three patients were also receiving the antiplatelet drug dipyridamole. No patient was using aspirin or other nonsteroidal anti-inflammatory agents. Most patients were anticoagulated for prosthetic heart valves and atrial fibrillation (Table 1) and extracapsular cataract extraction was the most frequent procedure performed (Table 2). The mean length of follow-up was 1.9 ± 1.3 years (range, four days to six years), with a preoperative prothrombin time determination made in 47 patients. The three patients in whom a prothrombin time was not measured within 24 hours of surgery all had a prothrombin time performed within one week before surgery.

Except for the patient having a combined penetrating keratoplasty and cataract extraction, all patients undergoing cataract surgery had a limbal-based incision. A peripheral iridectomy was performed in 24 cases and a sector iridectomy in three cases. No iridectomy was performed in the remaining 17 cases. One anterior chamber intraocular lens was placed after capsular rupture necessitating anterior vitrectomy. The remainder of the intraocular lenses were placed in the capsule or sulcus.

TABLE 1
INDICATION FOR LONG-TERM WARFARIN THERAPY

MEDICAL CONDITION	NO. OF PATIENTS*
Prosthetic heart valve	26
Atrial fibrillation	18
Ischemic heart disease	2
Ischemic vascular disease	9
Repeated venous thromboembolism	6

*Total number of indications for warfarin therapy exceeds 50 because some patients had more than one indication.

Anticoagulant therapy was continued in nine patients. The procedures included seven extracapsular cataract extractions with posterior chamber intraocular lens placement, an anterior orbitotomy, and a trabeculectomy. In one patient undergoing extracapsular cataract extraction with intraocular lens placement in whom preoperative prothrombin time was not measured the prothrombin time seven days before surgery was 18.2 seconds; no perioperative complications occurred. Among the other eight patients, the mean preoperative prothrombin time was 19.7 ± 5.2 seconds (range, 13.2 to 24.7 seconds). Two hemorrhagic complications occurred in this group. A large subconjunctival hemorrhage occurred at the beginning of the trabeculectomy and the surgery was canceled. The preoperative prothrombin time in this patient was 24.7 seconds. Warfarin dosage was decreased and the procedure was performed without hemorrhagic complications two weeks later. The other complication was a 25% hyphema that was noted on the first postoperative day after extracapsular cataract extraction, peripheral iridectomy, and placement of a sulcus-fixed posterior chamber intraocular lens. The patient was hospitalized and observed for five days during which time the hyphema resolved spontaneously. The preoperative prothrombin time was 15.7 seconds. No thrombotic complications were noted in this group of patients.

In the other 41 patients, warfarin therapy was discontinued a mean of 5.5 days before surgery (range, three to 19 days). Dipyridamole was continued in those patients already receiving it. Warfarin therapy was resumed from one to 14 days postoperatively (mean, 1.8 days). Intravenous heparin was used perioperatively in ten patients for a mean of seven days (range, three to 12 days). None of the patients

TABLE 2
PROCEDURES PERFORMED AND RESULTING HEMORRHAGIC COMPLICATIONS IN PATIENTS RECEIVING LONG-TERM ANTICOAGULANT THERAPY

		WARFARIN CONTINUED (9 PATIENTS)		WARFARIN DISCONTINUED (41 PATIENTS)	
PROCEDURE	NO. OF PATIENTS	NO HEMORRHAGIC COMPLICATIONS	HEMORRHAGIC COMPLICATIONS	NO HEMORRHAGIC COMPLICATIONS	HEMORRHAGIC COMPLICATIONS
Extracapsular cataract extraction/ intraocular lens	40	6	1	30*	3
Extracapsular cataract extraction	3	0	0	2	1
Penetrating keratoplasty/ extracapsular cataract extraction	1	0	0	1	0
Penetrating keratoplasty	1	0	0	1	0
Trabeculectomy	1	0	1	0	0
Anterior orbitotomy	1	1	0	0	0
Vitrectomy	2	0	0	2	0
Scleral buckle	1	0	0	1	0
Total	50	7	2	37	4

*One thrombotic complication occurred in this group.

who received heparin had hemorrhagic or thrombotic complications. Vitamin K and fresh-frozen plasma were administered to one patient each.

In two patients undergoing extracapsular cataract extraction with intraocular lens placement, preoperative prothrombin time was not measured. The first patient had a prothrombin time of 17.8 seconds six days preoperatively and warfarin was discontinued three days before surgery. The other patient had a prothrombin time of 16.1 seconds seven days preoperatively and warfarin was discontinued six days before surgery. Warfarin therapy was resumed on the first postoperative day in both patients and no hemorrhagic or thrombotic complications occurred.

Among those patients in whom a preoperative prothrombin time was measured, the mean prothrombin time before discontinuation of warfarin was 19.4 ± 5.9 seconds (range, 14.5 to 42.2 seconds); preoperatively it was 12.3 ± 3.9 seconds (range, 10.4 to 17.2 seconds). Thus, although warfarin was discontinued, several surgeons elected to perform operations in some instances while the prothrombin time was still increased. Among the patients undergoing cataract surgery, two sector iridectomies and 22 peripheral iridectomies were performed. Four hemorrhagic complications occurred in this group. Among patients not having a peripheral iridectomy, three intraoperative hyphemas occurred during cataract surgery; one required irrigation and the other two resolved spontaneously. Preoperative prothrombin values in these patients were 11.9, 12.6, and 14.2 seconds (the patient with a prothrombin time of 11.9 seconds was also receiving dipyridamole). The other complication was bleeding after iridectomy in one patient with a preoperative prothrombin time of 17.2 seconds; irrigation was required to clear the hemorrhage. The one thrombotic complication noted in this group was a thrombosed popliteal artery aneurysm seen on the first postoperative day after cataract surgery. This patient had also been receiving dipyridamole preoperatively. The thrombosis resolved with intravenous heparin therapy over seven days.

None of the 50 patients in the control group experienced hemorrhagic or thrombotic complications.

There was a significant difference in hemorrhagic complications after ocular surgery in the anticoagulated compared to the control group ($P < .03$). No significant difference was found

when comparing those patients in whom warfarin was continued to those in whom it was discontinued. There appeared to be a tendency for increasing complications with an increase in the prothrombin time, but it was not significant. None of the patients with perioperative complications experienced an adverse visual result because of the bleeding. All had a final visual acuity of better than 20/40.

Discussion

Little has been written about the local and systemic complications occurring in patients who undergo ophthalmic surgery while receiving anticoagulant therapy. Guidelines have not been defined that direct the ophthalmologist in managing anticoagulation therapy before, during, or after ophthalmic surgery.

Tinker and Tarhan[2] reviewed 180 noncardiac operations in 159 patients with prosthetic heart valves. In 153 operations (86%), warfarin therapy had been discontinued preoperatively. No thrombotic complications were noted for two years postoperatively in this group of patients. They concluded that there was minimal risk to stopping oral anticoagulants one to three days preoperatively and reinstituting it one to seven days postoperatively.

Katholi, Nolan, and McGuire[3] performed a prospective study of noncardiac surgery in patients with prosthetic heart valves. In patients with aortic valve prostheses warfarin was discontinued for three to five days without heparin, whereas in patients with mitral valves or multiple prosthetic valves perioperative heparin was used. No thrombotic complications were noted in either group.

Kulvin[5] reported implanting iris clip or iris plane lenses in 68 patients who were receiving anticoagulant therapy. Anticoagulants had been discontinued for at least five days before and resumed seven days after surgery. No hemorrhagic complications were noted in any of his patients. No mention of thrombotic complications or preoperative prothrombin times was made.

Hall, Steen, and Drummond[6] performed intracapsular cataract surgery in 13 patients (16 eyes) without cessation of anticoagulants. Medallion intraocular lenses were implanted in ten cases. The preoperative prothrombin time was increased in 13 cases. One patient had a 2-mm hyphema that resolved spontaneously and another patient died three months postoperatively of a myocardial infarction.

Stone, Kline, and Sklar[7] performed a survey of members of the American Intraocular Implant Society regarding their approach to patients receiving anticoagulation therapy. Although most favored discontinuing anticoagulant agents perioperatively, ten surgeons (7.4% of respondents) favored continuing warfarin therapy. Interestingly, no hemorrhagic complications were reported by the group who continued the warfarin therapy. Those who discontinued warfarin reported numerous hemorrhagic complications varying from incisional bleeding and hyphemas to retinal and expulsive choroidal hemorrhages. No explanation for this unusual finding was offered. Thrombotic complications, including two deaths secondary to cerebrovascular accidents, were also noted among those patients in whom warfarin was discontinued. It was not recorded when these thrombotic complications occurred in the perioperative period.

McMahan[8] performed 26 extracapsular cataract procedures with intraocular lens placement and placed two secondary anterior chamber intraocular lenses in 22 anticoagulated patients continued on therapy. An age-matched control was operated on on the same day. Compared to controls, there was an increase in eyelid ecchymoses and subconjunctival hemorrhages, which were believed to be clinically insignificant. There were also three hyphemas (all less than 15%) that resolved spontaneously in the anticoagulated group. No mention of thrombotic complications or preoperative prothrombin values was made.

In our study there was a significant increase in hemorrhagic complications comparing the warfarin sodium-treated group to the control group. The lack of significant difference found between patients in whom anticoagulation was continued and those in whom it was discontinued must be viewed with caution since the number of patients is small and several patients in whom anticoagulants had been discontinued still had an increased prothrombin time preoperatively. It is noteworthy that two patients with normal preoperative prothrombin times experienced hemorrhagic complications. This may relate to the different rate of synthesis of vitamin K-dependent factors when warfarin is discontinued. Prothrombin is factor II. However, the standard laboratory test for prothrombin time reflects both the presence of factor II and factor VII. Factor VII has a short half-life

TABLE 3
HALF-LIFE OF VITAMIN K-DEPENDENT FACTORS INFLUENCED BY WARFARIN THERAPY

FACTOR	HALF-LIFE (HRS)
II	60
VII	6
IX	24
X	40

and is synthesized more rapidly than factor II (Table 3).[9] Thus, factor VII levels return to normal more rapidly after discontinuation of warfarin. The term prothrombin time as measured by the prothrombin test is misleading because the test is more sensitive to levels of factor VII than of factor II. Because of this imbalance of resynthesis of vitamin K-dependent factors after discontinuation of warfarin, the prothrombin time may return to normal levels before adequate amounts of prothrombin have been synthesized. Therefore, prothrombin values that are obtained soon after warfarin has been discontinued must be interpreted cautiously.[10,11] Unfortunately, determination of actual levels of factor II are not routinely available and, thus, the prothrombin test remains the most practical means of estimating the coagulation status of a patient.

Our study is subject to numerous potential errors. The study was retrospective and some patients may have been missed. The procedures were performed by numerous surgeons. In comparing patients receiving warfarin to the controls, there was a significant difference in the number of patients with cardiac and neurologic illnesses, which may have contributed to the increased surgical complication rate. Finally, the number of patients involved was small, especially in the group in which warfarin was continued, and it is not possible to conclude how best to treat these patients on the basis of this study.

Despite these shortcomings, some conclusions can be made. There were six perioperative hemorrhagic complications in the warfarin-treated patients (12%) compared to none in the control group, which was statistically significant ($P < .03$). These complications, however, had no long-term effect on visual acuity. Among the nine patients undergoing surgery in whom the anticoagulants were not discontinued, there were no thrombotic complications in the postoperative period. Only one thrombotic complication was noted among the 41 patients in whom the anticoagulants were discontinued, and this was a popliteal arterial thrombosis that was effectively treated with heparin. Finally, prothrombin times measured after warfarin has been discontinued must be interpreted cautiously as they may not accurately reflect the levels of all vitamin K-dependent factors. After discontinuation of warfarin, a bleeding complication related to incomplete recovery of vitamin K-dependent factors can still occur despite a normal prothrombin time value.

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Positron Emission Tomography to Study the Effect of Eye Closure and Optic Nerve Damage on Human Cerebral Glucose Metabolism

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We used ^{18}F-2-fluoro-2-deoxyglucose and positron emission tomography to evaluate the effect of visual deprivation on brain glucose metabolism. In experiment 1, we compared local cerebral metabolic rates for glucose in seven normal volunteers studied with eyes closed to 11 age- and sex-matched normal volunteers studied with eyes open. Whole brain metabolism was similar in the two groups, and region/whole brain analysis of metabolic data showed that metabolism in the calcarine posterior cortex was decreased by 14% ($P < .05$) with eye closure. Glucose metabolism in other regions was not different between the two groups.

In experiment 2, we compared glucose metabolism in six patients with severe bilateral optic neuropathies to 12 age- and sex-matched normal controls. Whole brain glucose metabolism was unchanged in the optic neuropathy group compared to controls. However, statistically significant reductions in glucose metabolism in the optic neuropathy group were found in anterior calcarine cortex (17%), posterior calcarine cortex (27%), peristriate cortex (27%), and lateral occipital cortex (15%). The metabolic effects of damage to the pregeniculate visual system went well beyond those of simple eye closure.

Accepted for publication May 1, 1989.

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THE AFFERENT VISUAL SYSTEM is ideal for studying human cortical metabolic activity because the type of afferent input and the degree of clinical deficit can be defined more objectively than in other cortical lesions. Using ^{18}F-2-fluoro-2-deoxyglucose and positron emission tomography, we studied the effect on glucose metabolism in visual cortex of ischemic lesions affecting the occipital lobes and optic radiations[1,2] and of visual stimulation in normal subjects.[3] These and other positron emission tomography studies[4-8] have shown the following: (1) calcarine cortex metabolism responds in a graded fashion to increasingly complex visual stimuli, (2) calcarine and visual association cortex metabolism responds regionally to hemifield visual stimulation in a fashion predictable by known neuroanatomic pathways, (3) calcarine cortex ischemia results in reduced glucose metabolism in cortical areas appropriate for visual field deficits, and (4) optic radiation ischemia produces more modest reductions in calcarine metabolic rate than infarction of the visual cortex itself. Cerebral metabolic studies in monkeys[9,10] have demonstrated a more widespread influence of visual stimulation on cerebral cortex (including portions of occipital, temporal, parietal, and frontal lobes) and subcortical structures (pulvinar, caudate, putamen, claustrum, amygdala).

We undertook this study to evaluate the effect of visual deprivation on human brain glucose metabolism. In experiment 1, we compared brain glucose metabolism in normal volunteers studied with eyes closed to those studied with eyes open. In experiment 2, we

evaluated the effect of severe bilateral optic neuropathy on brain glucose metabolism.

Material and Methods

Subjects and Experimental Design

Experiment 1—Eighteen healthy male volunteers were included in this study. All had a visual acuity of 20/30 or better in each eye, with no history of significant ophthalmologic or general medical disease. Seven individuals, with a mean age of 25 years (range, 20 to 31 years), were studied after having their eyes closed and blindfolded from ten minutes before isotope injection until scan completion. Eleven individuals, with mean age of 26 years (range, 18 to 35 years), were instructed to keep their eyes open throughout the study and to look at the ceiling of the dimly lit positron emission tomography room without a specific target.

Experiment 2—The subject group consisted of six patients with a visual acuity in each eye of 20/200 or poorer because of bilateral severe optic neuropathies (optic neuropathy group) of diverse origin and variable duration (Table 1). Clinical evaluation in each patient included complete neuro-ophthalmologic examination, Goldman kinetic perimetry, and computed tomography or magnetic resonance imaging, or both, within one month of positron emission tomography. In each case, neuro-ophthalmologic examination documented bilateral optic atrophy, abnormal pupillary reaction, and visual field loss diagnostic of bilateral optic neuropathy. In addition to pale optic nerves, Patient 3 had constricted visual fields and mild retinal pigmentary changes compatible with retinopathy as a remote effect of his lung cancer.[11,12] No patient had evidence of neurologic disease outside of the pregeniculate afferent visual system by history, symptoms, physical examination, or neuro-imaging. Positron emission tomography was performed with patients' eyes open.

TABLE 1
PATIENTS WITH OPTIC NEUROPATHY

PATIENT NO., AGE (YRS), SEX	DIAGNOSIS	DURATION (MOS)	VISUAL ACUITY*	
			R.E.	L.E.
1, 31, F	Optic neuritis	12	NLP	LP
2, 44, F	Optic neuritis	4	CF at 2 ft	CF at 2 ft
3, 73, M	Cancer-associated retinopathy syndrome	4	HM	HM
4, 69, F	Inflammatory chiasmal syndrome	11	20/400	20/800
5, 55, M	Glaucoma	36	20/200	NLP
6, 64, F	Glaucoma	36	NLP	CF at 6 ft

*NLP, no light perception; LP, light perception; HM, hand motions; CF, counting fingers.

Twelve normal volunteers of similar age and sex were selected as controls for positron emission tomography (mean age, 57 years; range, 27 to 73 years). Each normal volunteer had a visual acuity of 20/30 or better in each eye and no history of ophthalmologic or general medical problems. All 12 controls were studied with eyes open and were given the same instructions as patients in the optic neuropathy group.

Informed consent was obtained from each patient and control subject, and all procedures were approved by the Committee on Studies Involving Human Beings of the University of Pennsylvania. Participation in this study did not alter diagnostic or therapeutic plans of the responsible physicians.

Positron Emission Tomography

Each individual was studied in the quiet, dimly lit positron emission tomography laboratory. Fluorodeoxyglucose, 6 to 8 mCi, was injected 30 minutes before positioning the individual's head 20 degrees hyperextended from the orbitomeatal line in a modified PETT V scanner.[13] Data collection began 40 minutes after isotope injection, and brain images of local cerebral metabolic rates for glucose were obtained using the Phelps and associates'[14] modification of the method of Reivich and associates.[15] Characteristics of the positron emission tomography system and the data collection protocol have been described previously.[16,17]

Data Analysis

Regions of interest were placed on the metabolic images by a computerized overlay system based on normal human anatomy[18] as described previously.[3] Whole brain metabolic rates were calculated by two methods. Computed whole brain metabolic rates were obtained by the volume-weighted mean of metabolic rates of all regions of interest. Recovery whole brain meta-

bolic rates were calculated by assuming that the total brain radioactivity (total number of disintegrations detected during the positron emission tomography session) originated from one large region of interest.[19] Lobar metabolic rates were derived from metabolic rates for regions of interest within each lobe.

To reduce variability in glucose metabolism values between subjects, metabolic rates for each region of interest were normalized by the individual's computed whole brain value using the equation: normalized local cerebral metabolic rate = (local cerebral metabolic rate/computed whole brain metabolic rate) × 100. Statistical evaluation in each experiment was performed using Student's t-test for independent samples in anterior and posterior calcarine cortex, peristriate cortex (Brodman's regions 18 and 19), and lateral occipital cortex (visual association cortex). For experiment 2, statistical comparison by Student's t-test was also performed for lobar metabolic rates. The Bonferroni correction for multiple comparisons was not applied to these probability values.

TABLE 2

CEREBRAL GLUCOSE METABOLISM* IN EXPERIMENT 1

	EYES CLOSED		EYES OPEN	
AREA	LEFT	RIGHT	LEFT	RIGHT
Anterior calcarine cortex	109 ± 6	108 ± 8	107 ± 11	109 ± 9
Posterior calcarine cortex	94 ± 7‡	94 ± 5§	107 ± 12	109 ± 9
Lateral occipital cortex	90 ± 5	89 ± 5	91 ± 7	91 ± 4
Peristriate cortex	94 ± 10	97 ± 9	96 ± 14	100 ± 11
Whole brain†	6.29 ± 1.04		5.41 ± 0.84	

*Values shown as (regional glucose metabolism/computed whole brain glucose metabolism) × 100 ± S.D.

†Whole brain values by recovery shown as mg of glucose/100 g of brain/minute.

‡$P \le .05$.

§$P \le .01$.

Results

Experiment 1

Table 2 compares regional brain glucose metabolism in individuals studied with eyes closed to those studied with eyes open in visual cortex of four regions of interest in both hemispheres. Whole brain glucose metabolism was not different between eyes-closed and eyes-open groups (Table 2). Posterior calcarine cortex metabolism was 13% to 15% lower in the eyes-closed group ($P \le .05$), but changes in other brain regions were not statistically significant.

Experiment 2

Figure 1 shows typical positron emission tomography images from a control subject (Figure, left) and Patient 1 with bilateral optic neuritis (Figure, right). Relatively decreased glucose metabolism in calcarine, peristriate, and lateral occipital cortex was apparent in the patient with optic neuropathy.

Table 3 compares glucose metabolism of the optic neuropathy group to the eyes open control group in four visual regions of interest from each hemisphere. Whole brain glucose metabolism was unchanged in the optic neuropathy group compared to controls (Table 3). Statistically significant reductions in glucose metabolism in the optic neuropathy group were found in anterior calcarine cortex (17%), posterior calcarine cortex (27%), peristriate cortex (27%), and lateral occipital cortex (15%) when compared to controls. Table 4 shows lobar metabolic data for patients with optic neuropathy and controls. Occipital lobe metabolism was significantly decreased in the optic neuropathy group compared to that in the control group. Additionally, frontal lobe glucose metabolism was significantly increased in both hemispheres in patients with optic neuropathy (7%) compared to that in controls.

Discussion

In studying the metabolic effects of eye closure and of bilateral severe optic nerve disease, we found two different patterns of metabolic sequelae. Eye closure resulted in a mild decrease in posterior calcarine glucose metabolism, with no statistically significant changes in other brain areas. Bilateral optic nerve disease, on the other hand, was associated with relatively profound decreases in metabolism in areas of the cortex known to be responsible for vision. Clearly, these two different types of visual deprivation were not metabolically equivalent.

Control subjects for both experiments were

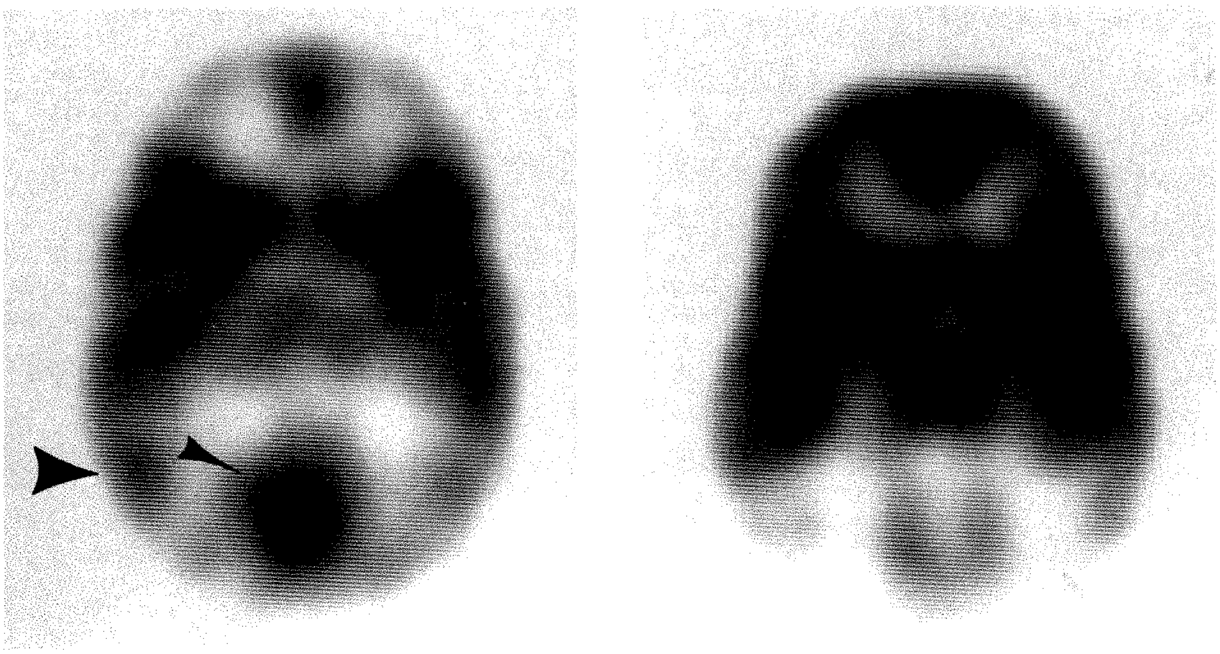

Figure (Kiyosawa and associates). Left, Positron emission tomography image from an eyes-open control subject at the level of the thalamus and superior primary visual cortex. Small arrow indicates area of greatest glucose uptake in posterior midline corresponding to calcarine (primary visual) cortex. Large arrow indicates lateral occipital (visual association) cortex. Right, Positron emission tomography image at same level as in Figure, left from Patient 1 in experiment 2 with bilateral severe optic neuritis without visual recovery. Primary visual cortex and visual association cortex have relatively low glucose uptake.

studied after lying quietly for 40 minutes with their eyes open looking at the ceiling of a dimly lit laboratory. Such a bland visual stimulus may cause little coordinated neural activity in the visual cortex, resulting in the minimal difference in visual cortex metabolism between individuals studied with eyes closed and those with eyes open in experiment 1.

In experiment 2, all areas of visual cortex in patients with optic neuropathy were significantly hypometabolic in a fashion that went well beyond the effects of the short-term visual

TABLE 3
CEREBRAL GLUCOSE METABOLISM* IN EXPERIMENT 2

	OPTIC NEUROPATHY GROUP		EYES OPEN GROUP	
AREA	LEFT	RIGHT	LEFT	RIGHT
Anterior calcarine cortex	103 ± 12‡	105 ± 7‡	124 ± 18	128 ± 19
Posterior calcarine cortex	81 ± 12§	85 ± 13§	122 ± 14	123 ± 18
Lateral occipital cortex	81 ± 10‡	85 ± 9‡	94 ± 10	96 ± 8
Peristriate cortex	76 ± 5§	79 ± 9§	101 ± 11	107 ± 12
Whole brain†	5.62 ± 1.77		4.92 ± 0.74	

*Values shown as (regional glucose metabolism/computed whole brain glucose metabolism) × 100 ± S.D.

†Whole brain values by recovery shown as mg of glucose/100 g of brain/minute.

‡P ≤ .05.

§P ≤ .001.

TABLE 4
LOBAR GLUCOSE METABOLISM* IN EXPERIMENT 2

	OPTIC NEUROPATHY GROUP		EYES OPEN GROUP	
LOBE	LEFT	RIGHT	LEFT	RIGHT
Frontal	114 ± 6†	116 ± 9†	107 ± 7	106 ± 8
Parietal	96 ± 12	93 ± 12	93 ± 7	91 ± 10
Temporal	88 ± 8	94 ± 9	92 ± 14	99 ± 9
Occipital	82 ± 6‡	86 ± 4‡	105 ± 7	108 ± 8

*Values shown as (regional glucose metabolism/computed whole brain glucose metabolism) × 100 ± S.D.

†P ≤ .05.

‡P ≤ .001.

deprivation in experiment 1. These patients had been visually deprived for a period of months or years (rather than 40 minutes), and increasing duration of sensory deprivation may have caused a progressive decline in visual cortex metabolism. However, metabolism of visual cortex did not correlate with duration of optic nerve damage within this small group of patients, and animal studies imply that recovery of cortical metabolism after permanent acquired deafferentation may be more common than a progressive decline in metabolism.[20-22]

The pregeniculate afferent visual system may have a specific coordinating or modulating effect on metabolism of the primary visual cortex that is independent of visual stimulation. For example, the pattern of electrical activity in the cat lateral geniculate body during eye closure reflects the pattern of ongoing electrical activity in the optic nerve.[23] This neural activity may play a role in priming the visual cortex to receive visual input, and the coordinating effect may be lost after damage to the pregeniculate afferent visual system. Alternatively, transsynaptic transfer of small molecules from pregeniculate afferent fibers to lateral geniculate neurons may have a trophic effect reflected in reduced visual cortex metabolism after optic nerve damage.[24]

Increased glucose metabolism in frontal cortex has not been reported previously with damage to the afferent visual system. This result was not anticipated, and uncontrolled factors in the study protocol may have resulted in spurious alterations in metabolism. Macko and coworkers[9] reported decreased frontal lobe metabolism ipsilateral to optic tract lesions in callosectomized monkeys. In addition to obvious differences in species and experimental technique, it may be important that these animals had intact vision in one homonymous visual field. The frontal cortex is involved in attention mechanisms,[25] and visual deficits in these patients may have required increased attention to spatial relations and physical activities or may have caused increased anxiety over the scanning process itself.[26] Electrophysiologic coordination between occipital and frontal lobes is obvious on electroencephalography,[27,28] and monosynaptic and polysynaptic subcortical connections between occipital and frontal lobes may have a predominantly inhibitory influence in certain circumstances.[29,30] Profound occipital hypometabolism in patients with optic neuropathy could permit frontal hypermetabolism by release of tonic inhibition.

Previous studies have shown that visual stimulation influences visual cortex metabolism.[3,5,6] We found that the level of visual stimulation is clearly not the only determinant of visual cortex metabolism because eye closure resulted in minimal metabolic changes whereas severe optic nerve damage was associated with profound decreases in metabolism throughout primary and association visual areas. Other determinants of visual cortex metabolism include the competence of the pregeniculate afferent system, the optic radiations,[1,32] and the calcarine cortex,[1,2] and perhaps other factors as yet unidentified. Visual stimulation or neural activity in the visual cortex may also have important effects on metabolism in the frontal cortex.

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Custom Orbital Implant in the Repair of Late Posttraumatic Enophthalmos

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We repaired late, posttraumatic enophthalmos in 21 patients by inserting a large, soft, Silastic block through a lower eyelid flap and transconjunctival approach to the orbit. These blocks were hand carved at the time of surgery to match bony defects as characterized by hypocycloidal tomographic biometry. Enophthalmos and hypo-ophthalmos were ameliorated with acceptable appearance in all cases. No implant rejections, migrations, or infections were found. Complications included upper eyelid blepharoptosis, lower eyelid retraction, and conjunctival prolapse. The improvements were stable over a median follow-up of 13 months.

In reviewing postmortem and x-ray studies of patients with enophthalmos, Pfeiffer in 1943[1] determined that disruption of the bony margins, specifically the floor of the orbit, was the cause of the enophthalmos. In 1944, King and Samuels[2] further elucidated the anatomic changes of the traumatized orbit. Finally, in 1957, Smith and Regan[3] experimentally recreated floor fractures and enophthalmos with hurled curling balls thrown at cadaver orbits and coined the term "blow-out fracture." Although most agree as to the anatomic basis of traumatic changes within the orbit, the timing, indications, and method of repair are varied.[4-10] Although most investigators agree that enophthalmos greater than 3 mm, particularly with accompanying hypo-ophthalmos or ocular dystopia (downward sinking of the eye), is a good indication for operative exploration and repair, the many methods described attest to the difficulty of this reconstruction. Repairs are accomplished with materials ranging from homografts of cartilage,[11] fascia,[12] and autogenous bone grafts,[13,14] to alloplastic materials including glass beads,[15] tantalum,[16] Teflon,[17] polyethylene,[18] methyl methacrylate,[19] and Silastic sheets.[20]

Most recently, techniques for greater reduction of bony volume and improved treatment of enophthalmos, including large osteotomies and mobilization of the walls of the oribit[21] and implantation of large alloplastic blocks,[22] have been reported. Herein we describe the development and results of a technique, first described in 1977,[23] that utilizes hand-carved, soft, Silastic blocks, which are customized to correct expansion of bony volume thought intrinsic and dominant in the pathophysiology of traumatic enophthalmos.[1,21-23]

Patients and Methods

Included in the study were 21 patients with computed tomographic-proven pure orbital floor fractures and late posttraumatic enophthalmos who were treated by us between 1977 and 1988. A minimum follow-up of one year was required for inclusion. All patients had similar surgery performed by the method described below, with the exception of Patients 1 and 2 in whom a transcutaneous approach to the orbit was used. The transconjunctival surgical approach was performed as follows.

After administration of general anesthesia, a 4-0 black silk suture was placed under the inferior rectus muscle insertion. A lateral canthotomy was accomplished with a full-thickness cut from lateral canthus to lateral

Accepted for publication April 18, 1989.

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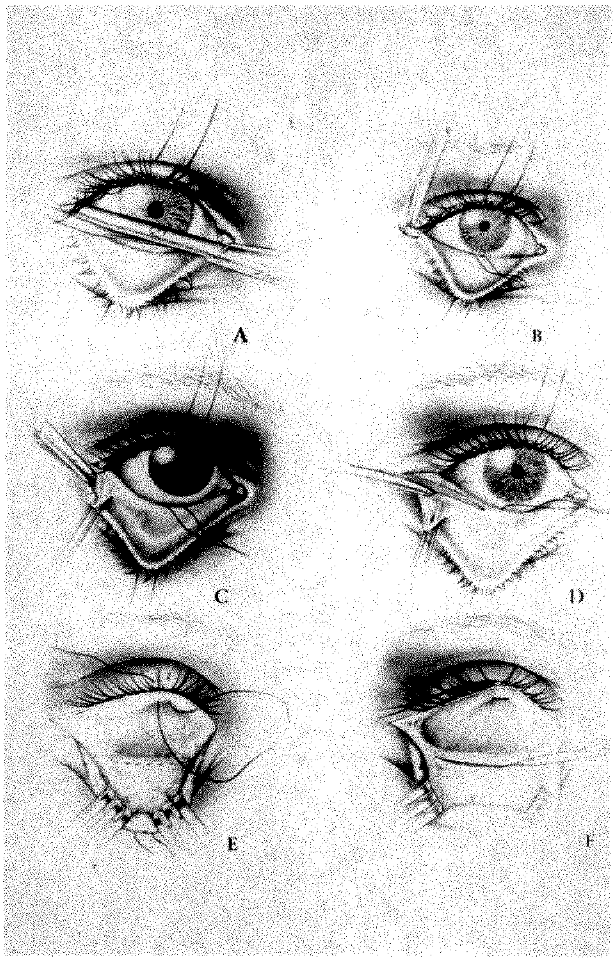

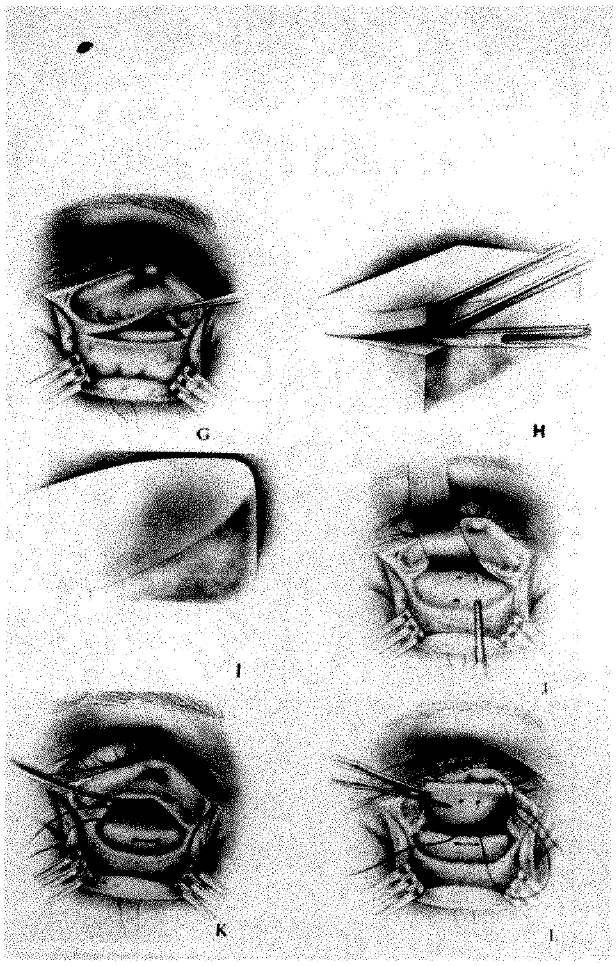

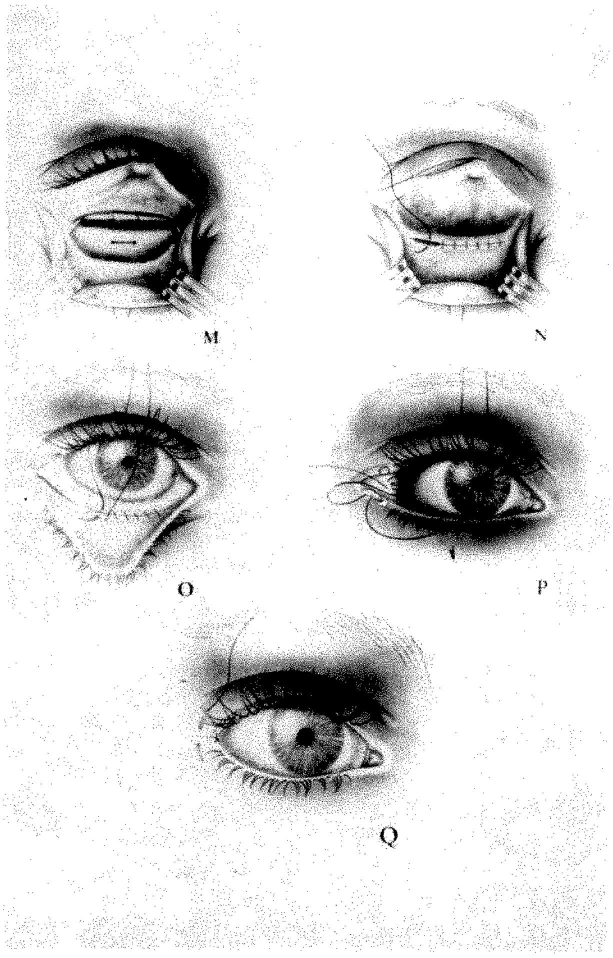

Fig. 1 (Putterman and Millman). A, Lateral canthotomy. B, Inferior crus cantholysis. C and D, Severing of the capsulopalpebral fascia. E, Exposure of the inferior orbital rim and periorbita. F, Incising the periorbita. G, Reflecting the periorbita. H, Carving the Silastic block. I, Finishing the custom implant. J, Drilling fixation holes. K, 2-0 polyfilament nylon suture placement. L and M, Suture fixation of the implant. N, Periorbital closure. O, Lower eyelid retractor repair. P, Lateral canthal tendon reapproximation to the lateral orbital rim. Q, Lateral commissure and lateral canthal repair.

orbital rim (Fig. 1, A). Orbicularis muscle was undermined from the anterior lower limb of the lateral canthal tendon and conjunctiva from the posterior aspect of the tendon. The lower limb of the tendon was then severed close to the lateral orbital wall (Fig. 1, B).

Next, the plane between orbicularis muscle and capsulopalpebral fascia was isolated (Fig. 1, C). Wescott scissors were passed through the lateral canthal opening until the tips were against the superior anterior surface of the tarsus. Since capsulopalpebral fascia, the analogue of the levator aponeurosis of the upper eyelid, is firmly attached to the anterior surface of the tarsus over its superior half, placement of the scissors in this portion should lead to the scissors being between orbicularis and capsulopalpebral fascia. The scissors were withdrawn, and one blade inserted, passed in the same plane anterior to the tarsus, and then slid to a position 3 mm above the inferior fornix. The scissors then severed conjunctiva, Müller's muscle, and capsulopalpebral fascia across the eyelid 3 mm above the inferior fornix (Fig. 1, D).

Next, a 4-0 black silk double-armed suture was passed through the cut edge of the inferior flap of conjunctiva, Müller's muscle, and capsulopalpebral fascia. Each arm was passed through the central gray line of the central upper eyelid, and tied (Fig. 1, E). Two rake retractors were hooked over the more superior aspect of conjunctiva, Müller's muscle, and capsulopalpebral fascia and used to pull the lower eyelid downward, exposing the inferior orbital rim. Any remaining orbicularis muscle or fascia over the orbital rim was severed with Wescott scissors until the periosteum of the orbital rim was visible. With a No. 15 Bard-Parker blade, an incision was made through periosteum several millimeters beneath the inferior orbital rim and across the eyelid (Fig. 1, F). This maneuver was facilitated by holding a periosteal elevator over the inferior orbital rim to ensure its position.

The sharp edge of a Tenzel periosteal elevator was used to reflect periosteum from its tight adherence to the inferior orbital rim (Fig. 1, G). The blunt end of the elevator was then used to reflect periosteum from the orbital floor. Any adhesions of the orbital contents to the orbital floor were bluntly released with the periosteal elevator or cotton-tipped applicators. When it is necessary to cut these tissues to free the orbital contents from the orbital bone, it is important to place a suture under the inferior rectus muscle and pull the inferior rectus suture upward to locate the posterior extent of the inferior rectus muscle in the orbit. This maneuver facilitates the severing of orbital tissues without injuring the inferior rectus muscle.

The next step of the procedure concerns carving an orbital floor implant from a soft 155-mm Silastic block (Fig. 1, H) with a No. 10 Bard-Parker blade. The shape of the implant was determined preoperatively by studying anteroposterior, and lateral tomographic orbital x-ray films. The magnified size of these films was considered in determining the position of the fractured orbital floor compared with the normal level of the floor. Also calculated was the number of millimeters the eye was displaced downward (hypo-ophthalmos) by holding a ruler level with the medial canthi and noting where the ruler bisected each eye. Tomographic assessment and measurements of the degree of hypo-ophthalmos aid in determining the needed thickness and shape of the orbital floor implant. The implant is generally carved so that it is 2 to 3 mm thick anteriorly and increases in thickness as it extends posteriorly. Usually, the thickness beneath the eye is equivalent to the millimeters of downard displacement, and the posterior aspect is several millimeters thicker than this (Fig. 1, I). The contour of the implant and its medial and lateral thickness are determined by the shape of the fractured orbital floor. During the carving, the implant was positioned over the orbital floor to judge the level of the eye, the intraocular pressure, and the upward movement of the eye with the inferior rectus suture. If the eye appeared markedly higher than the other eye, the intraocular pressure substantially increased, or if the inferior rectus muscle was entrapped, the implant was removed and carved to obtain a perfect fit.

Two drill holes were placed over the central, inferior orbital rim. A dental drill fit with a wire-passing burr penetrated bone 3 mm beneath the central inferior orbital rim and exited through the orbital floor approximately 8 mm posterior to the inferior orbital rim (Fig. 1, J). A malleable retractor reflects periosteum and protects the globe while irrigating solution is sprayed onto the field during the drilling. A 2-0 polyfilament nylon suture without a needle was then passed through each hole in the inferior orbital rim hole and out the holes in the orbital floor (Fig. 1, K). Each arm of the suture was then passed through a cutting needle. The

needle then penetrated the anterior surface of the carved implant, passing from the superior anterior surface and exiting at the posterior surface approximately 7 mm posterior to the anterior rim of the implant (Fig. 1, L). When these suture ends were drawn up and tied, the anterior aspect of the implant was displaced downward, allowing the posterior aspect of the implant to elevate slightly (Fig. 1, M). This not only pushes the eye upward but pushes it outward slightly. The polyfilament sutures were tied with approximately four to five knots, and the ends were cauterized with disposable cautery to form a bulbous tip, which decreases the chance of slippage. The knots lie beneath the orbital implant (Fig. 1, M).

The level of the eye was again observed, the intraocular pressure checked, and the upward movement of the eye tested. If the results were satisfactory, the periosteum was sutured over the inferior orbital rim with interrupted polyglactin 910 4-0 sutures (Fig. 1, N).

The edges of the conjunctiva, Müller's muscle, and capsulopalpebral fascia were connnected with a 5-0 chromic catgut suture run continuously across the eyelid in a nasal to temporal direction (Fig. 1, O). A 4-0 double-armed polypropylene suture was passed through the lower limb of the lateral canthal tendon in an internal to external direction. Each arm of the suture passes through periosteum of the lateral orbital wall and exits over the lateral orbital rim (Fig. 1, P). Positioning of the suture in this manner not only connects the temporal aspect of the eyelid to the lateral orbital wall but also places it more posteriorly. A 4-0 polyglactin 910 suture was also used to connect the most posterior extent of the lateral canthal tendon to periosteum and to cover the polypropylene knot. The remainder of the wound was closed with 5-0 polyglactin 910 interrupted orbicularis sutures and a continuous 6-0 black silk suture (Fig. 1, Q).

The inferior rectus muscle suture was removed and a 4-0 black silk suture passed through skin and orbicularis over the central lower eyelid several millimeters beneath the eyelashes. The other arm of the suture was passed through similar tissue in the upper eyelid. The suture was tied initially with a surgeon's knot and then with a shoelace-type loop. In this way, the eyelid can close, but the suture also can be released during the postoperative period for inspection of the eye. A light pressure dressing was applied. Systemic antibiotics were initiated intraoperatively and were continued for one week postoperatively. Visual acuity was checked as soon as the patient was awake, and it was rechecked multiple times during the next 24 hours.

Results

Twenty-one patients, 14 men and seven women, were included in the study. Patients showed the typical demographics of the traumatic patient population, with most being young and male. The patients ranged in age from 22 to 39 years. Surgery was performed from four months to ten years from the date of injury (median, eight months; mean, 20 months). The fracture defects as determined by life-scale measurements on hypocycloidal tomography were large. The vertical and horizontal depths of the fracture and proposed implants were determined preoperatively. The defects and their corresponding implants averaged horizontally in the anterior orbit 24 mm and in the posterior orbit 16 mm, with depths (or floor depression) of 4 mm anteriorly and 8 mm posteriorly. The average volume represented was equal to 3.2 cc, or approximately 10% of orbital volume expansion (based on an average orbital volume of 30 cc).[24,25]

Success was judged subjectively by physician and patient. No reoperations were indicated and satisfactory cosmesis was achieved in all cases. The Table gives enophthalmic and hypoophthalmic findings and results.

Significant complications included four residual upper eyelid blepharoptoses and two lower eyelid retractions, with one case of lateral telecanthus thought to be secondary to inadequate wound closure. There were no implant migrations or infections.

The motility of all patients improved. In three patients diplopia in the central binocular field preoperatively resolved postoperatively. Thirteen patients had general enlargement or improvement of their binocular fields. No patient experienced deterioration of their binocular fields. One patient (Patient 13) with a 12-prism diopter hypotropia preoperatively improved to 5 prism diopters, but subsequently underwent successful extraocular muscle surgery to correct the traumatic paresis (proven by abnormal forced generation test) responsible for the residual hypotropia.

TABLE
ENOPHTHALMIC AND HYPO-OPHTHALMIC RESULTS

PATIENT NO.	SURGICAL DELAY (MOS)	COMPLICATIONS	AMOUNT OF ENOPHTHALMOS (MM)	CHANGE IN AMOUNT OF ENOPHTHALMOS (MM)	AMOUNT OF HYPO-OPHTHALMOS (MM)	CHANGE IN AMOUNT OF HYPO-OPHTHALMOS (MM)
1	4	Lower eyelid retraction	3	1	4	2
2	6	Lower eyelid retraction	4	8.5	5	5
3	6	None	6	1.5	3	2
4	8	None	4	2	4	4
5	24	Blepharoptosis	0.5	1.5	2.5	3.5
6	12	None	7.5	2	5	5
7	8	None	1	2.5	2	2
8	120	None	4.5	3	4	2
9	5	Blepharoptosis	5	3	3	3
10	12	None	5	2	4	4
11	16	Telecanthus	4	3	3	3.5
12	3	None	8	6	2	2
13	84	None	4	3	5	4
14	7	None	3.5	2.5	2	3
15	5	Conjunctival prolapse	6	4	3.5	4
16	24	None	12	6	5	3
17	15	Blepharoptosis	4	2.5	4	2.5
18	84	None	8	5	5	5
19	4	None	4	2	2	2
20	8	Blepharoptosis	6	3	3	4
21	72	None	5	2	3	2

Discussion

Our results demonstrate the acceptability of large, carved Silastic blocks as an orbital implant. Alloplastic materials in carefully structured series have proven to have no greater incidence of complications than autogenous bone grafts. The incidence of complications is reported to be 0.0053% per year after the first postoperative month.[24] Early complications within the first month are thought to be related to lack of fixation of the implant, causing migration and packing of the sinus, thereby causing infection. Histopathologic studies of silicone and other alloplastic implants confirmed good tolerance in the orbit.[25]

Enophthalmos has experimentally and clinically been demonstrated to be mainly the result of expansion of the bony volume of the orbit, with some contribution to retraction of the globe secondary to entrapped orbital contents (that is, extraocular musculature and orbital fascial planes). Little evidence supports fatty necrosis as contributory to volume changes.[23] We believe the use of dissection of the periorbita and freeing of incarcerated orbital contents in our technique, combined with cubic centimeter per cubic centimeter of reduction of bony volume and reconstruction of suspensory support of the globe, is well suited to reversal of the disease process of enophthalmos.

As shown in the Table, the main cosmetic defect in traumatic enophthalmos was more related to the level of hypo-ophthalmos, inferior vertical displacement of the globe, than enophthalmos, axial displacement of the globe. Patients 3, 5, and 7 had a minimal degree of enophthalmos. All patients had significant hypo-ophthalmos, however, with a mean of 3.5 mm and a median of 4.0 mm. Seventeen patients attained within 1 mm of relative hypo-ophthalmos as compared with only eight patients who attained less than 2 mm of anteroposterior axial disparity. This indicates that complete correction was therefore most consistently related to full correction of hypo-ophthalmos rather than enophthalmos. This

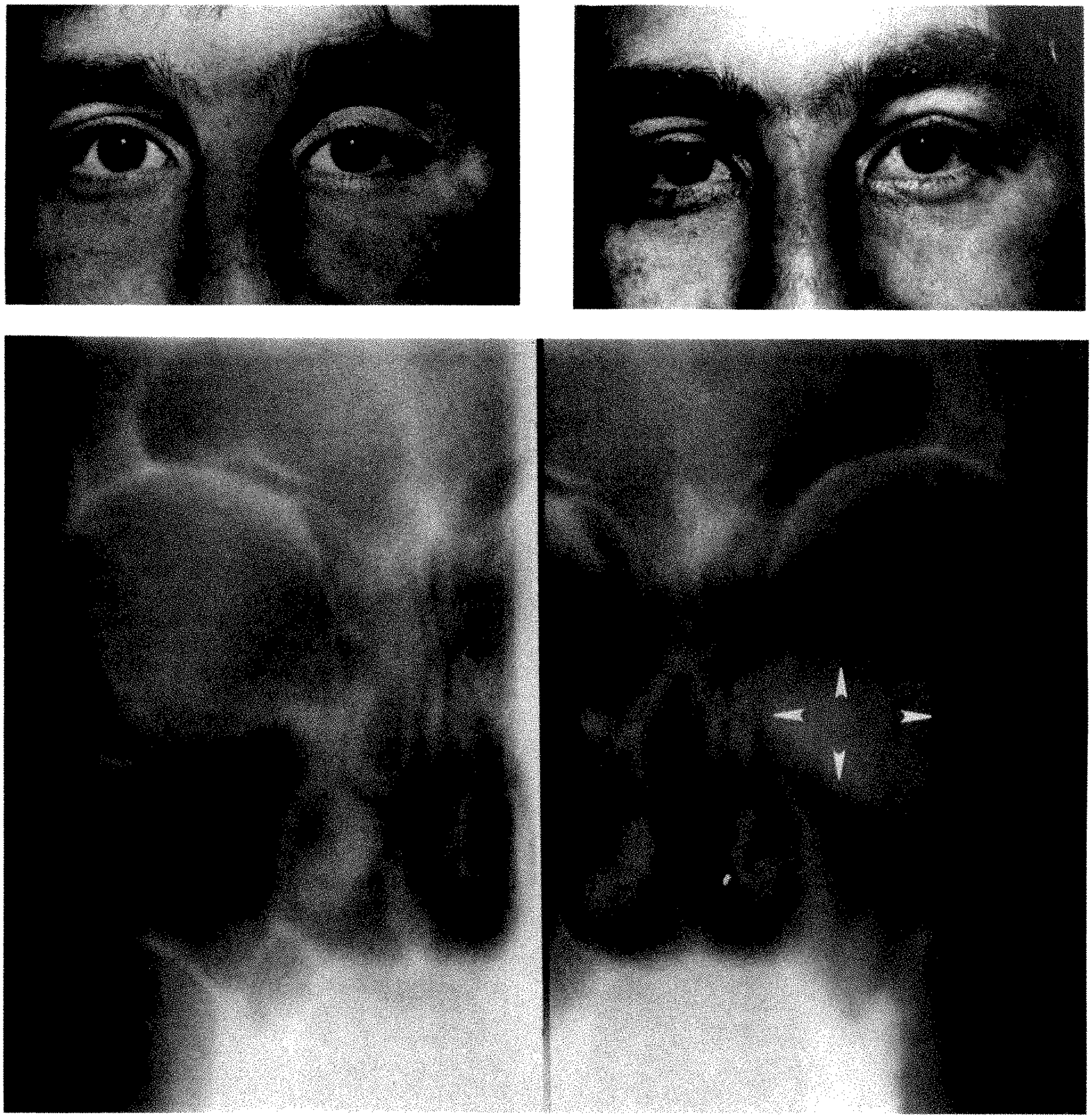

Fig. 2 (Putterman and Millman). Top left, Properative photograph. Note left enophthalmos, hypo-ophthalmos, and superior sulcus deformity. Top right, Postoperative photograph with complete resolution of enophthalmos, hypo-ophthalmos, and superior sulcus deformity. Bottom, Hypocycloidal tomogram of vertical and horizontal dimensions outlined (arrowheads).

implies that anatomic reestablishment of the suspension of the globe in its proper vertical axis was more significant cosmetically and functionally than axial displacement. The carved Silastic blocks placed both under and behind the globe may act to support the compromised suspensory ligaments in the orbit that are thought to play a large role in the development of enophthalmos in the traumatized orbit.[24] This resuspension of the globe probably accounts for the normalization of the superior sulcus deformity also.

All secondary eyelid malpositions were easily corrected with a second procedure. It is likely in the patients with blepharoptosis that the correction of hypo-ophthalmos frequently unmasked a traumatic blepharoptosis. It is also expected that the degree of trauma to create these orbital deformities resulted in a significant incidence of damage to the levator muscle and caused secondary blepharoptoses. All blepharoptoses were corrected and resolved with either conjunctival Müller muscle resection or levator aponeurosis surgery.[23] The two lower eyelid retractions both occurred early in the series and were both associated with transcutaneous approaches. This approach was replaced with the transconjunctival, transfornix approach described herein. The severe eyelid retraction was thought to be secondary to both the transcutaneous technique and the large implants used initially. Patient 2 was overcorrected. All lower eyelid retractions, however, responded well to vertical lengthening by means of capsulopalpebral fascial recessions and bank scleral grafting.[23]

Preoperative and postoperative photographs of Patient 4 show excellent global position with resolution of enophthalmos and hypo-ophthalmos and superior sulcus deformity (Fig. 2). Results of motility examination were further improved with enlargement of the patient's binocular field.

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Medial and Lateral Wall Decompression for Thyroid Ophthalmopathy

Charles R. Leone, Jr., M.D., Ken L. Piest, M.D., and Richard J. Newman, M.D.

A two-wall decompression of the orbit, consisting of removal of the medial and lateral walls, was successful in eight patients with thyroid ophthalmopathy. The lateral wall was by removed by using the standard orbitotomy technique in addition to enlarging the space with a pneumatic burr, and the medial wall was removed through a direct medial canthal incision. Two patients had optic neuropathy, one had intermittent subluxation of the globe, and five had symptoms of exposure or increased pressure in the orbital area. In our eight patients, the two with optic neuropathy improved, the patient with subluxation of the globe became asymptomatic, and the other five had less exposure and were more comfortable. The amount of decompression ranged between 4 and 7 mm. The lacrimal sac was injured in one patient; temporary silicone intubation avoided any permanent sequela.

GRAVES' DISEASE continues to frustrate ophthalmologists and internists with its complex array of manifestations and unpredictable clinical course. Graves' disease can be treated medically, surgically, and with irradiation. When surgical decompression is indicated, a one- to four-wall decompression procedure using a variety of approaches may be used, each with its own advantages and associated complications.[1-5] Frequently, the orbital floor is removed either alone or in conjunction with a medial wall decompression. This is an effective procedure, but complications involving extraocular muscle imbalance, infraorbital nerve anesthesia, hypo-ophthalmia, and recurrent sinusitis are common.[6,7] We used a combined medial and lateral wall decompression procedure that was effective in reducing exophthalmos and relieving optic nerve compression while minimizing complications associated with the procedures involving the removal of the floor of the orbit.

Material and Methods

The procedure was performed after administration of general anesthesia. The patient was placed in a reverse Trendelenburg position to reduce venous pressure to the head. The middle meatus was packed with three cottonoids soaked with cocaine 4%. The medial canthal and temporalis fossa areas were injected with 0.5% bupivacaine hydrochloride with 1:200,000 epinephrine hydrochloride. Intermarginal sutures made of 6-0 silk over 5-mm #40 silicone band pegs were placed between the eyelids to protect the globe. The lateral wall decompression was performed first. An incision was made from the lateral canthus into the temporalis fossa for approximately 4 to 6 cm (Fig. 1). Care must be taken not to extend the incision too far laterally to avoid injuring the frontal branch of the facial nerve. The lateral orbital rim was exposed and a vertical incision made in the periosteum, which was separated from the rim and the periorbita reflected from the lateral wall. With a malleable retractor inserted on the inner aspect of the wall to protect the orbital contents, a reciprocating saw was used to remove the lateral orbital rim. The bone cuts were at the level of the zygomatic arch and just above the zygomatic-frontal suture (Fig. 2). This allows removal of a 20- to 25-mm segment of bone. A rongeur was used to grasp the rim between the bone cuts and bend it backward, breaking it free from the posterior bone (Fig. 3). The rongeur is then used to remove the thin

Accepted for publication May 11, 1989.
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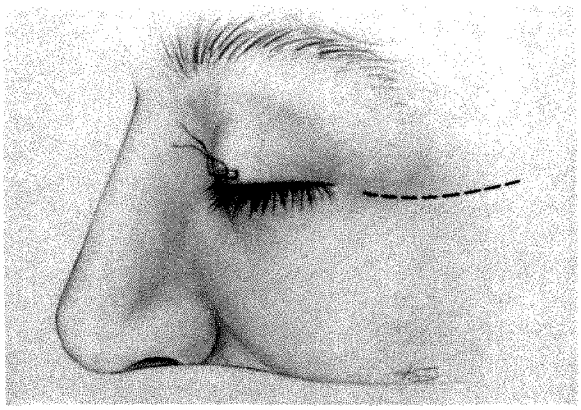

Fig. 1 (Leone, Piest, and Newman). An incision is begun 5 mm from the lateral canthus into the temporalis fossa area for 4 to 6 cm. An intermarginal suture of 6-0 silk is placed through #40 silicone band pegs to protect the globe.

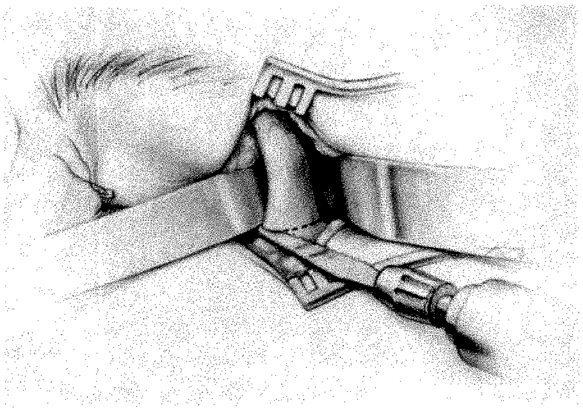

Fig. 2 (Leone, Piest, and Newman). After the lateral rim has been exposed, a malleable retractor is inserted on the inner aspect of the lateral wall to protect the orbital contents. A reciprocating saw makes bone cuts at the level of the zygomatic arch and just above the zygomatic-frontal suture line.

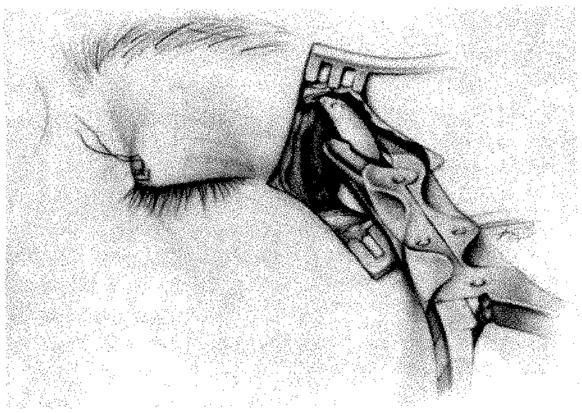

Fig. 3 (Leone, Piest, and Newman). A rongeur is used to grasp the rim between the cuts and bend it backward, breaking it off at the thinner posterior wall.

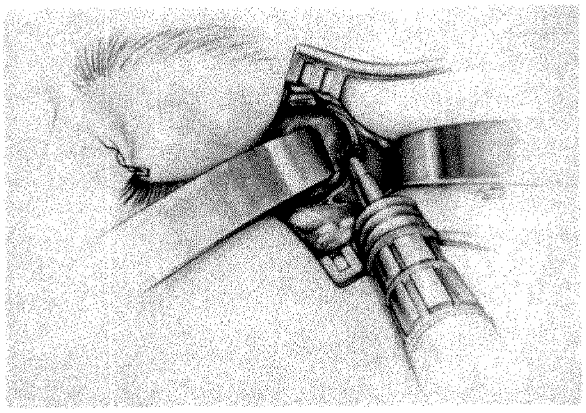

Fig. 4 (Leone, Piest, and Newman). After the thinner bone of the lateral wall is removed with rongeurs, a 5-mm burr on an air drill is used to enlarge the entire opening, particularly in the area of the thicker sphenoid bone.

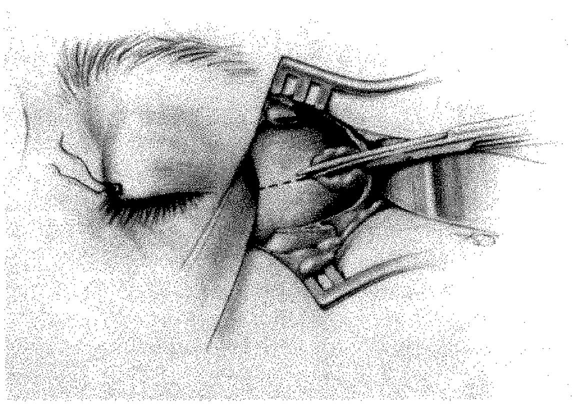

Fig. 5 (Leone, Piest, and Newman). The periorbita is incised, allowing the fat to prolapse.

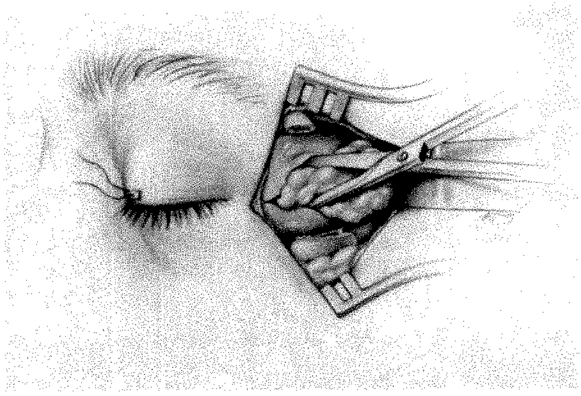

Fig. 6 (Leone, Piest, and Newman). The fat is gently spread to break the fine septa, allowing it to prolapse more freely into the temporalis fossa.

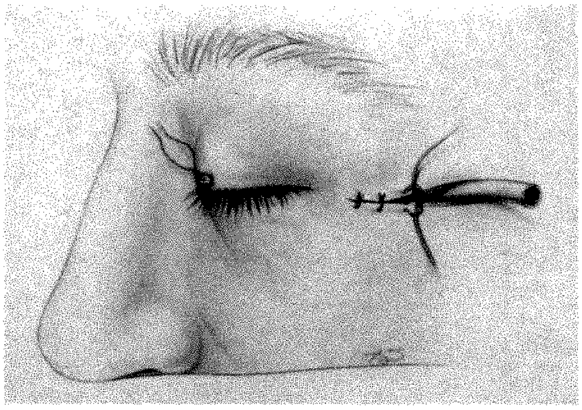

Fig. 7 (Leone, Piest, and Newman). A Penrose drain is inserted into the area of decompression to eliminate fluid accumulation. The subcutaneous layer is closed with 5-0 chromic catgut and the skin with the same or 5-0 polypropylene.

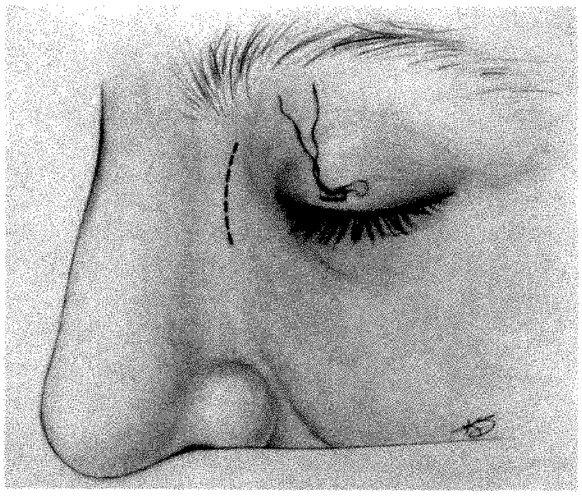

Fig. 8 (Leone, Piest, and Newman). An incision is made in the medial canthus down to the periosteum approximately 1 cm from the canthal angle.

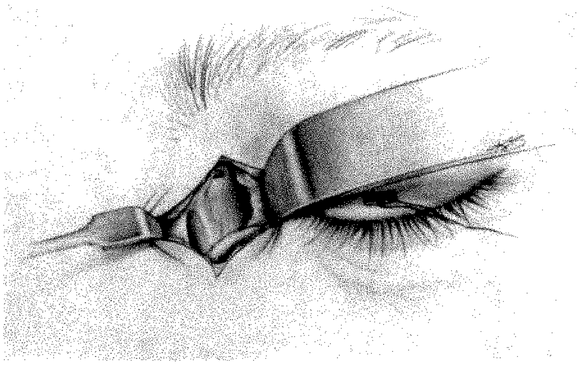

Fig. 9 (Leone, Piest, and Newman). The medial canthal tendon together with the lacrimal sac are reflected laterally. The anterior ethmoidal artery is identified, coagulated, and severed.

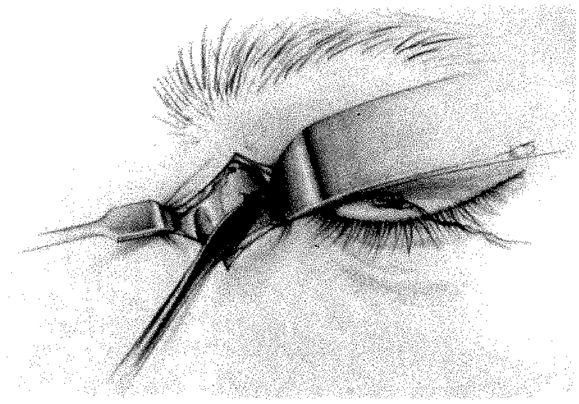

Fig. 10 (Leone, Piest, and Newman). The ethmoid sinus is entered, with firm pressure applied to a periosteal elevator.

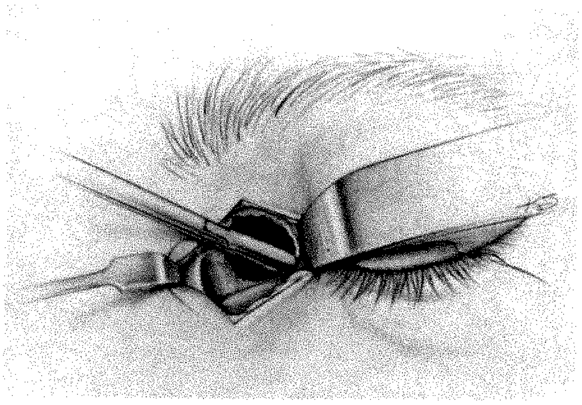

Fig. 11 (Leone, Piest, and Newman). Using the ethmoidal artery as a landmark, the bone is removed from just behind the posterior lacrimal crest to the area of the posterior ethmoidal artery. The mucosa and the air cells are obliterated followed by externalization of the ethmoid sinus into the middle meatus.

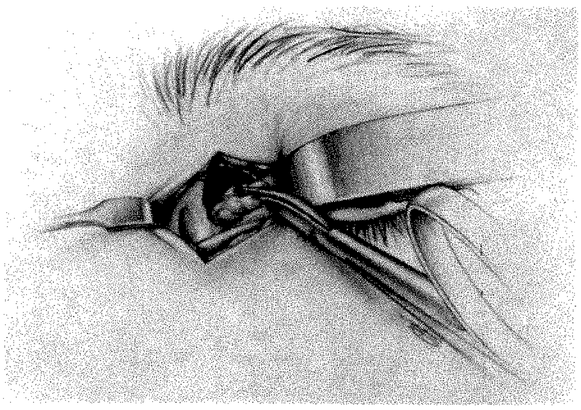

Fig. 12 (Leone, Piest, and Newman). The periorbita is incised with scissors beginning posterior to the lacrimal sac and taken as far back as the medial wall removal. Gentle spreading of the fat can be done to enhance prolapse of the orbital tissue into the sinus.

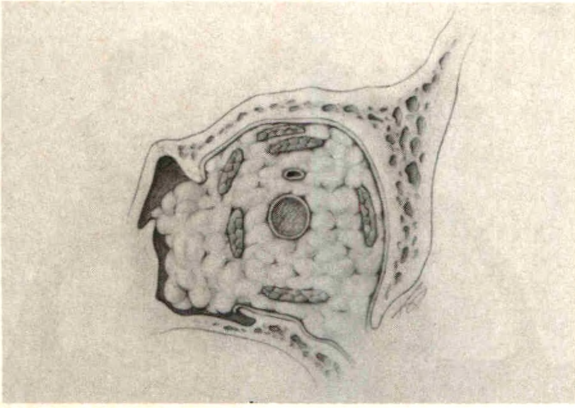

Fig. 13 (Leone, Piest, and Newman). A coronal section through the retrobulbar space demonstrates the prolapse of the fat into the ethmoid sinus.

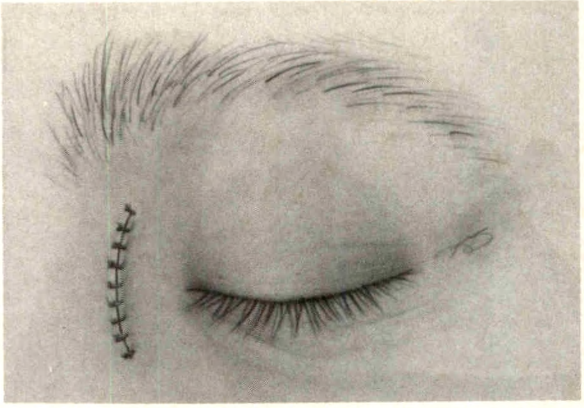

Fig. 14 (Leone, Piest, and Newman). The subcutaneous tissue and skin are closed with 5-0 chromic catgut suture.

bone of the lateral wall until the thicker sphenoid bone is reached. A pneumatic drill with a 5-mm burr was used to remove more of the bone to enlarge the bony window. The thicker sphenoid bone can be removed almost to the point of reaching the dura, further enlarging the decompressive space (Fig. 4). The periorbita was then incised (Fig. 5) and scissors were used to spread the fat gently to break the fine septa, allowing it to prolapse more easily into the temporalis fossa (Fig. 6). Only the subcutaneous tissues and skin were closed, and a Penrose drain was left in the temporalis fossa to eliminate any fluid accumulation (Fig. 7).

The medial decompression was begun with a slightly curved incision in the medial canthal area adjacent to the medial canthal tendon and was extended far enough vertically to expose the entire medial wall (Fig. 8). After the periosteum was incised and the medial canthal tendon reflected, the lacrimal sac was retracted laterally and the medial wall exposed (Fig. 9). The anterior ethmoidal artery was identified and coagulated and used as a landmark for the superior extent of the medial wall removal, since the intracranial cavity lies above the ethmoidal arteries. The ethmoid sinus was entered with firm pressure applied with a periosteal elevator (Fig. 10). A Takahashi biting forceps or Kerosin punch was used to remove the bone piece by piece (Fig. 11). The air cells were obliterated and the mucosa removed as well. The ethmoid sinus was then externalized into the middle meatus with a hemostat, followed by the placement of a Telfa roll that extended to the external nares. The decompression was not taken beyond the posterior ethmoidal artery to avoid injury to the optic nerve. The periorbita was incised with scissors beginning just posterior to the lacrimal sac and taken to the posterior extent of the decompression (Figs. 12 and 13). The lacrimal system was irrigated to make certain that the sac was not inadvertently ruptured; if injury had occurred, indwelling silicone tubes were inserted. The subcutaneous tissue and skin were closed with 5-0 chromic catgut suture (Fig. 14). During the procedure, the patient was given 4 mg of dexamethasone and a cephalosporin antibiotic intravenously; both drugs were continued postoperatively for 24 hours and then given orally for seven to ten days. The Telfa nasal pack was removed on postoperative day 1 and the Penrose drain was removed from the lateral incision after 48 hours.

Results

Eight patients underwent medial and lateral orbital decompression. Four patients had bilateral procedures, giving a total of 12 eyes. The patients ranged in age from 47 to 68 years. There were five women and three men. Two patients had optic neuropathy. One was a 68-year-old woman with a visual acuity of 20/400 in the right eye and a depressed visual-evoked potential. Her postoperative visual acuity was 20/70+ and her visual-evoked potential was improved. The other was a 47-year-old man who had a preoperative visual acuity of 20/20 in the left eye, disk edema, and an enlarged blind spot. Postoperatively, his visual acuity improved to 20/20+, his disk edema resolved, and

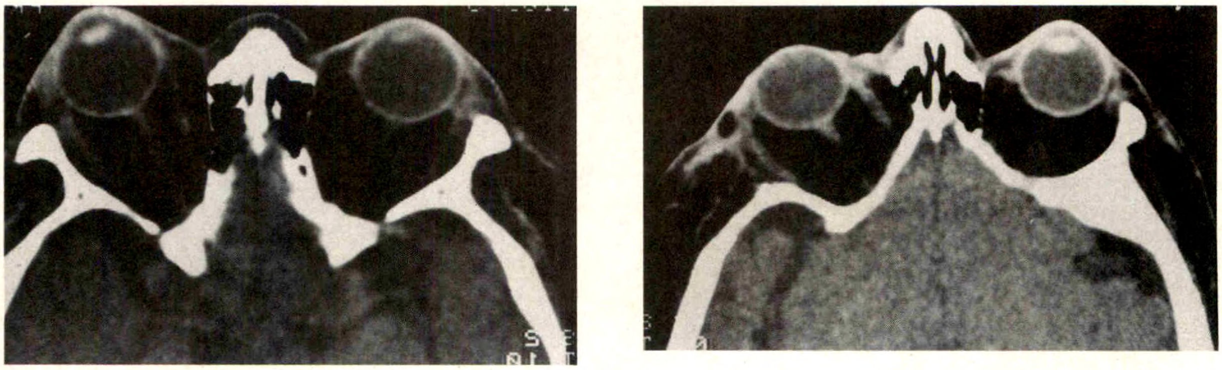

Fig. 15 (Leone, Piest, and Newman). Left, Preoperative axial computed tomography of patient who had intermittent subluxation of right globe between her eyelids. Right, Postoperative scan showing prolapse of the orbital tissues into the lateral and medial decompressive spaces.

his blind spot returned to almost normal size. A 49-year-old woman who had intermittent subluxation of the right globe between the eyelids underwent a successful 5-mm decompression. The remaining patients, who all had symptoms of exposure keratopathy, improved postoperatively. The amount of decompression ranged from 4 to 7 mm (average, 5.6 mm). There was no change in extraocular muscle movement in any patient.

Discussion

Currently, the most common types of decompression techniques include removal of the orbital floor with or without the medial wall either by the transeyelid, inferior fornix, or transantral approaches, and the three-wall decompression which includes the lateral wall. The lateral wall decompression alone has not been believed to be effective unless combined with one of the other procedures, particularly in cases of compressive optic neuropathy.[8,9] However, the computed tomographic scan in our patient who had intermittent subluxation of the right eye shows a significant prolapse of tissue into the temporalis fossa (Fig. 15). The four-wall decompression, which includes the orbital roof, can be used in extreme cases but requires the assistance of a neurosurgeon. In a four-wall decompression, a large portion of the sphenoid bone is removed in the apex of the orbit and the lateral one half of the orbital roof is removed, exposing the dura.[3]

Whenever the floor is included in the decompression procedure there is the potential for extraocular muscle imbalance, hypo-ophthalmia, infraorbital nerve damage, and maxillary sinusitis.[6,10] Losing the inferior support to the orbital tissues could cause a disturbance in motility, particularly if there was already compromise or restriction in muscle movement preoperatively. Diplopia in the primary position that had not been present preoperatively has been reported in up to 30% of cases in which some restriction was present before surgery.[7] Hypo-ophthalmia is the most difficult problem to manage and can be associated with motility problems because of the vertical misalignment or dropping of the globe. Moreover, it is a noticeable cosmetic deformity and can cause flattening of the supratarsal space of the upper eyelid. The muscle imbalance can be addressed with either prisms or muscle surgery. Hypo-ophthalmia requires a challenging orbital reconstructive procedure to raise the level of the globe with an implant to that of the opposite eye. Although every effort is made to preserve the neurovascular bundle, traction on the infraorbital nerve can cause partial or complete malfunction postoperatively. There is usually some infraorbital nerve anesthesia postoperatively, which disappears after several months. If function does not return, it can be disconcerting to the patient. Maxillary sinusitis is a common sequela since the sinus drains into the middle meatus, and pooling of old blood and secretions in the sinus floor can cause infection. This can be avoided by creating a nasal-antral window into the inferior meatus at the time of decompression to allow for gravitational drainage.

Because of the potential problems, we strove to achieve a satisfactory decompression from

both a functional and cosmetic standpoint while avoiding the floor of the orbit. In addition to removing the lateral rim and the thin portion of the lateral wall, using a high speed burr allows one to carry the decompression more posteriorly through the thick sphenoid bone. This not only relieves more pressure from the apex of the orbit but enlarges the decompression area. Although the temporalis muscle occupies the area into which the lateral decompression is occurring, it provides far less rigidity than the bony lateral orbital wall. After the periorbita is cut, gentle spreading of the fat with blunt scissors breaks the fine septa allowing the fat to prolapse more freely into the lateral space (Fig. 15). The lateral rim was not replaced in any of our patients and has not resulted in a cosmetic blemish.[11,12] In 45 lateral decompressions done by Long and Ellis,[13] removing the lateral orbital rim was of no cosmetic significance. The potential complications in doing the lateral orbitotomy include damaging the frontal branch of the seventh cranial nerve if the incision is taken too far posteriorly, scarring, lymphedema from interruption of the lymphatic drainage, and a possibility of entering the cranial cavity.

The direct medial canthal approach avoids the eyelids, and this eliminates the possibility of eyelid malposition.[14,15] With an ample incision and exerting careful traction against the lacrimal sac, adequate exposure of the wall can be obtained even to the area of the posterior ethmoidal air cells. This is particularly important in cases of optic neuropathy, since the greatest pressure from the enlarged extraocular muscles is near the apex of the orbit. We do not, however, routinely go beyond the posterior ethmoidal artery since it would bring us perilously close to the optic nerve. Moreover, it is important to keep the bony extirpation below the level of the ethmoidal vessels to preclude entering the anterior cranial fossa and producing a possible cerebral spinal fluid leak. Lacrimal injury is always a potential problem because of the prolonged traction over the sac in attempting to obtain maximum exposure in an orbit that is already compromised. Lacrimal irrigation should be carried out at the end of the procedure to ensure its patency and to uncover any possible rents.[16,17] In cases of lacrimal sac injury, silicone tubes should be inserted. Damage to the trochlea is a possibility as well, but if one avoids penetrating the periorbita in the anterior aspect of the superomedial quadrant, this complication should be rare.

After approximately 4 to 7 mm of decompression, none of our patients lost vision or had worsening of extraocular muscle movement. This is the same amount of decompressive effect that has been reported with the antral-ethmoidal and three-wall approaches; yet, we have had none of the frequently encountered complications associated with those approaches as a result of removing the orbital floor. Two patients in our series had an improvement in their vision: visual acuity in a patient with optic neuropathy improved from 20/400 to 20/70−, and a patient with optic disk edema had resolution of the edema over a three-month period. It is difficult to measure the exact amount of decompression since a Hertel exophthalmometer does not give a valid reading in eyes with the lateral rim removed. Nevertheless, assessment of the position of the globe in relationship to the nose and superior rim from side photographs has allowed us to make estimates as to the number of millimeters of decompression. The only significant complication in our eight patients was injury to a lacrimal sac, which required silicone intubation for several months. When the tube was removed, irrigation was easily accomplished and the system has remained patent.

The goal of any decompression is to maximize the decompressive effect to save vision or protect the eye while minimizing side effects. Our technique of medial and lateral decompression eliminates removing the orbital floor, which is the cause of most complications. The eyelids and fornix are spared incisions, which eliminates eyelid malposition. This technique leaves the orbital floor intact, thus providing support for the orbital contents and lessening the chance for extraocular muscle imbalance, hypo-ophthalmia, sinusitis, and infraorbital nerve damage.

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OPHTHALMIC MINIATURE

According to the theoretical view proposed by Thomas Young and more fully developed by Helmholtz, the eye perceives but three colors or wavelengths, and all the other colors and shades known to us arise from the compound of the primary ones in the eye. The light waves are received by a layer of the retina, called the rods and cones, where experiments have led investigators to believe that the sensation of sight is located. The layer is named for the shapes assumed by the optic nerve substance there, which is supposed to be tuned to the reception of color vibrations.

Scientific American, April 1875

Angiolymphoid Hyperplasia With Eosinophilia of the Orbit Associated With Obstructive Airway Disease

Scott B. Sheren, M.D., Philip L. Custer, M.D., and Morton E. Smith, M.D.

Two patients with angiolymphoid hyperplasia with eosinophilia isolated to the orbit had eyelid swelling, a superior orbital mass, and histories of intermittent obstructive airway disease. One patient later developed a transient peripheral blood eosinophilia as high as 36%. One lesion recurred 38 months postoperatively and responded to systemic corticosteroid therapy.

ANGIOLYMPHOID HYPERPLASIA with eosinophilia manifests as a benign tumor usually about the head and neck. The lesions may be isolated or multiple, and vary in clinical appearance from skin papules to subcutaneous nodules. Histopathologically, the lesions are composed of vascular hyperplasia with plump endothelial cells accompanied by varying degrees of mixed cellular infiltrate dominated by lymphocytes and eosinophils.[1] In the dermatologic and pathologic literature, this entity is described under various names, including eosinophilic granuloma of soft tissue, inflammatory angiomatous nodule, atypical pyogenic granuloma, histiocytoid hemangioma, epithelioid hemangioma, and Kimura's disease.[1-6] Angiolymphoid hyperplasia with eosinophilia is rare in the orbit; eight histopathologically proven cases of isolated orbital disease have been described in the English language literature.[7-12]

Case Reports

Case 1

A 57-year-old black man had a three-day history of progressive, painful swelling of the left upper eyelid. There was no history of trauma. One month earlier the patient had been hospitalized because of dyspnea and bronchospasm, which responded promptly to systemic corticosteroids and aminophylline therapy.

On examination visual acuity with pinhole was 20/100 in the left eye. Swelling of the left eyelids (Fig. 1), a palpable soft tissue mass in the superolateral orbit, and preauricular adenopathy were noted. Supraduction and abduction were limited. Computed tomography demonstrated a soft tissue mass conforming to the globe, with no change in the adjacent bone (Fig. 2). Idiopathic orbital inflammatory syndrome was suspected; biopsy and debulking of the lesion were performed through an anterior orbitotomy. The histopathologic diagnosis was angiolymphoid hyperplasia with eosinophilia (Fig. 3). After a course of systemic corticosteroids, cyclophosphamide was given, but there was no change in the residual soft tissue mass. The patient was left with mild limitation of abduction.

Three months after the initial examination, the patient was again hospitalized with bronchospasm. The bronchospasm responded to therapy. Peripheral blood eosinophilia levels ranged from 10% to 36%.

Thirty-eight months after the orbital biopsy, the patient again developed left upper eyelid swelling and 10 mm of left proptosis. The mass lesion was again palpable and supraduction was markedly limited. On a regimen of 80 mg of prednisone per day, the clinical signs completely resolved over four weeks. After slowly tapering the corticosteroid therapy, the patient has remained asymptomatic for 12 months.

Case 2

A 77-year-old Oriental woman had a one-week history of painless, progressive swelling of the right upper eyelid. She denied a history of trauma, and except for asthma controlled with aminophylline and terbutaline, she was in good health. Visual acuity was 20/50 in each eye as a result of age-related macular degenera-

Accepted for publication May 1, 1989.
From the Department of Ophthalmology and Visual Sciences, Washington University School of Medicine, St. Louis, Missouri. This study was supported by an unrestricted grant from Research to Prevent Blindness, Inc.
Reprint requests to Morton E. Smith, M.D., Department of Ophthalmology, Washington University School of Medicine, 660 S. Euclid Ave., St. Louis, MO 63110.

Fig. 1 (Sheren, Custer, and Smith). Case 1. Marked left upper and lower eyelid swelling.

tion. She had vitiligo of the skin of her eyelids, right upper eyelid swelling (Fig. 4), and a nontender mass palpable in the superolateral orbit.

Computed tomography showed the lesion molding to the surface of the globe (Fig. 5). After biopsy and debulking, 80 mg of triamcinolone was injected into the residual lesion. Postoperatively, the mass was no longer apparent on clinical examination. Histopathologic study confirmed angiolymphoid hyperplasia with eosinophilia. Twenty-two months postoperatively, the patient remained asymptomatic.

Discussion

The wide spectrum of histopathologic features of angiolymphoid hyperplasia with eosinophilia may lead to its confusion with a variety of benign and malignant tumors, including Kaposi's sarcoma, epithelioid hemangioendothelioma, reaction to insect bite, pyogenic granuloma, angiomatous lymphoid hamartoma, meningioma, granuloma faciale, and eosinophilic granuloma.[8,9] As indicated by Hidayat and associates[9] this entity must also be distinguished from angiosarcoma, which is characterized by intraluminal budding of atypical endothelial cells, increased mitotic activity, necrosis, and the absence of marked tissue eosinophilia.

Fig. 2 (Sheren, Custer, and Smith). Case 1. Soft tissue mass molding the globe.

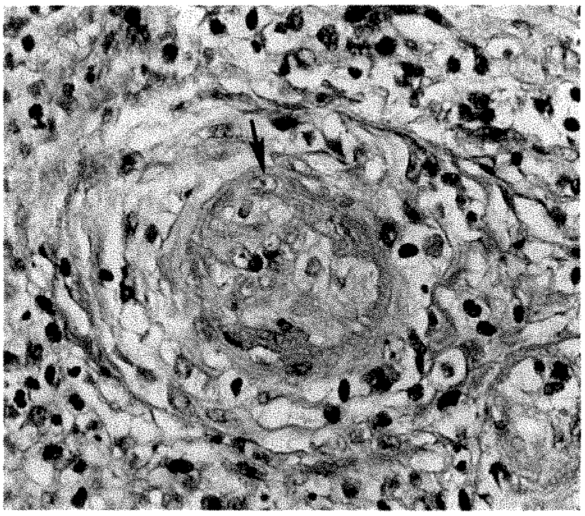

Fig. 3 (Sheren, Custer, and Smith). Central blood vessel with plump endothelial cells (arrow) surrounded by lymphocytes and eosinophils (hematoxylin and eosin, ×100).

In 1948, Kimura, Yoshimura, and Ishikawa[13] described an entity they termed an "unusual granulation combined with hyperplastic changes of lymphatic tissue," which other investigators agree fits within the histopathologic spectrum of angiolymphoid hyperplasia with eosinophilia.[1-4] Lymphadenopathy and peripheral blood eosinophilia are features of Kimura's disease.[13] In one review of patients with angiolymphoid hyperplasia with eosinophilia, three of 16 patients (19%) had regional lymphadenopathy and four of 20 (20%) had peripheral blood eosinophilia.[1] Takenaka and associates[7] reported a case of orbital disease in their series in which the initial peripheral blood eosinophil count was 40%. They also found increased levels of serum IgE and serum anti-*Candida* IgE antibody in their patients. Our Patient 1 had peripheral blood eosinophilia ranging from 10% to 36%. We did not measure serum IgE levels in our patients. An association between this entity and bronchial asthma has been documented.[14,15]

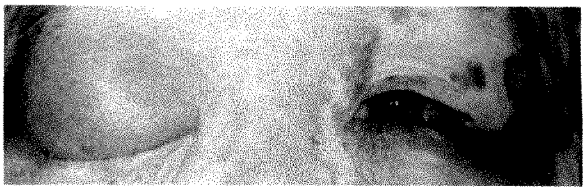

Fig. 4 (Sheren, Custer, and Smith). Case 2. Marked right upper eyelid swelling.

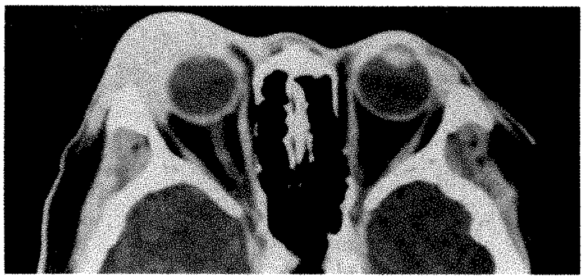

Fig. 5 (Sheren, Custer, and Smith). Case 2. Orbital mass molding the globe.

In a review of the English language literature, Henry and Burnett[4] described 171 cases of angiolymphoid hyperplasia with eosinophilia and characterized the lesions within racial groups. Of the patients described, 117 were Oriental, 46 were white, seven were black, and three were Middle Eastern. They found that large, painful or pruritic tumors were more likely to be found in black or Middle Eastern patients, whereas Oriental patients were more likely to have large (greater than 2 cm) tumors and to remain asymptomatic.

Angiolymphoid hyperplasia with eosinophilia occurring in association with an Iowa enucleation implant has recently been reported.[10] Orbital disease may be preceded by other foci of involvement, as illustrated by angiolymphoid hyperplasia with eosinophilia of the lacrimal gland in a patient with contralateral parotid infiltration.[11] Angiolymphoid hyperplasia with eosinophilia involving the parotid gland is well documented.[6,11] In our patients, the lesions were found in the superior orbit and involved the lacrimal gland fossa. The lacrimal gland may be the initial site of involvement in some patients.

Hidayat and associates[9] concluded that the treatment of choice for this condition appears to be complete surgical excision when possible. Both of our patients responded to corticosteroids.

Although angiolymphoid hyperplasia with eosinophilia may represent a vascular neoplasm with secondary inflammatory features, these lesions probably represent a reactive inflammatory process to some undetermined stimulus. Occurrence adjacent to an enucleation implant, association with increased serum IgE levels, and the association with peripheral blood eosinophilia as well as intermittent obstructive airway disease, support a reactive origin for this disorder.

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Treatment of Postvitrectomy Fibrin Pupillary Block With Tissue Plasminogen Activator

Glenn J. Jaffe, M.D., Hilel Lewis, M.D., Dennis P. Han, M.D., George A. Williams, M.D., and Gary W. Abrams, M.D.

We injected 25 μg of recombinant tissue plasminogen activator into the anterior chamber or the vitreous cavity in seven aphakic patients for pupillary block caused by a complete fibrin pupillary membrane that formed after vitrectomy with fluid-gas exchange. Progressive fibrin deposition resulted in pupillary block by three days after vitrectomy surgery in six patients, and seven days after vitrectomy in one patient. The pupillary block was associated with increased intraocular pressure in six patients. Tissue plasminogen activator was injected via the corneoscleral limbus in five patients and via the pars plana in two patients. In all patients, injection of tissue plasminogen activator resulted in complete fibrinolysis of the fibrin pupillary membrane within four hours, associated with a deepening of the anterior chamber. In the six patients with increased intraocular pressure at the time of tissue plasminogen activator injection, dissolution of the fibrin membrane was associated with a decrease in pressure. In all patients, intraocular pressure had returned to normal by three days after the injection. No complications were associated with the injection.

THE EFFICACY OF recombinant tissue plasminogen activator for the treatment of postvitrectomy fibrin[1] and for filtering bleb thrombolysis in patients after glaucoma surgery[2] has been recently reported. Additionally, tissue plasminogen activator has been used to treat hyphema, fibrin formation, vitreous hemorrhage, suprachoroidal hemorrhage, and branch retinal artery occlusion in experimental animal models.[3-9] Herein, we describe the use of human recombinant tissue plasminogen activator in the treatment of fibrin pupillary block after vitrectomy surgery and intraocular gas injection.

Accepted for publication May 9, 1989.
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Material and Methods

From February 1988 to February 1989, we injected recombinant tissue plasminogen activator into the anterior chamber or vitreous cavity of seven patients who developed fibrin pupillary block after vitrectomy surgery (Table). Six of seven patients received 0.5 ml of subconjunctival dexamethasone sodium phosphate (24 mg/ml) at the conclusion of the surgical procedure in an effort to decrease postoperative inflammation. Despite periocular corticosteroid injection, anterior chamber fibrin formation was apparent by slit-lamp examination on the first postoperative day in each case. Six patients were treated hourly with topical corticosteroids in an attempt to prevent further fibrin formation. Fibrin deposition progressed in all patients, however, and by three days, six patients had developed pupillary block caused by occlusion of the pupil by the fibrin membrane. This membrane characteristically appeared as a sheet of semitranslucent to opaque material that spanned the entire pupil, and usually prevented detailed visualization of the retina. The pupillary block was initially treated by argon laser membranolysis in one patient (Patient 3), but fibrin reformation resulted recurrent pupillary block one day later. In one patient (Patient 7) a fibrin membrane spanning

the pupil had formed by three days after surgery without an associated pupillary block. In this patient, 25 μg of tissue plasminogen activator injected into the anterior chamber resulted in dissolution of the fibrin membrane. The fibrin membrane recurred, however, and on the seventh day, fibrin occluded the pupil, which caused pupillary block glaucoma.

In six patients, pupillary block was characterized by iris bombé, with closure of the anterior chamber angle as determined by gonioscopy and a formed but shallow anterior chamber centrally. In one patient (Patient 4), pupillary block was accompanied by complete iridocorneal apposition with a flat central chamber. In none of the patients did the chamber deepen with face-down positioning to move the bubble posteriorly.

Intraocular pressure was measured preoperatively and at least once daily postoperatively. Postoperative pupillary block was accompanied by increased intraocular pressure not responsive to maximal medical management at the time of tissue plasminogen activator injection in six patients (Table). Intraocular pressure was measured one hour after injection, and daily thereafter. No eyes had rubeosis at the time of injection.

Approval for intraocular tissue plasminogen activator was obtained before beginning this study from the Human Research Committee at the Medical College of Wisconsin and from the Review Board at the Jules Stein Eye Institute. Written informed consent was obtained from each patient before administration of intraocular tissue plasminogen activator. The tissue plasminogen activator was prepared for intraocular use, and was administered as previously described.[1] Briefly, 50 mg of lyophilized recombinant tissue plasminogen activator was reconstituted in 50 ml of sterile water, per the manufacturer's recommendations. The drug was then diluted fourfold with sterile balanced saline solution, divided into multiple individual aliquots in a sterile laminar flow hood, and stored for future use at −70 C in an ultralow freezer. We then injected 25 μg of the reconstituted and diluted tissue plasminogen activator via the corneoscleral limbus in eyes receiving anterior chamber injections and via the pars plana in eyes receiving vitreous cavity injections. The following case report was chosen to illustrate the typical course and treatment of patients who received tissue plasminogen activator for postvitrectomy fibrin pupillary block.

Case Report

A 50-year-old man sustained multiple facial and orbital fractures in a motor vehicle accident. He was initially seen because of decreased visual acuity in the right eye. His ocular and medical history was unremarkable. On examination, visual acuity was R.E.: light perception and L.E.: 20/20. In the right eye, the intraocular pressure was 1 mm Hg by pneumotonometry and there was a severe afferent pupillary defect. On slit-lamp examination, the anterior one third of the cornea showed mild anterior stromal thinning with a superficial opacity. The anterior chamber had 2+ flare and no cells. There was no rubeosis. The lens had moderate nuclear sclerosis. There was a dense vitreous hemorrhage that obscured the view of the retina. By ultrasound, there was a total retinal detachment of the right eye. Results of examination of the left eye were normal.

The patient was brought to the operating room and underwent pars plana vitrectomy and lensectomy. After the vitreous hemorrhage had been cleared, the patient was found to have a total retinal detachment with proliferative vitreoretinopathy. An occult posterior scleral rupture was also found, with retinal and uveal tissue incarcerated in the scleral wound. Membranes were stripped from the retina, and a limited retinectomy was performed to free the incarcerated retina. A scleral buckle, fluid-gas exchange with 20% perfluoropropane, and laser endophotocoagulation of the right eye were then performed.

On the first postoperative day, intraocular pressure was 37 mm Hg in the right eye. There was a complete fibrin pupillary membrane with a shallow anterior chamber superiorly and a normally formed anterior chamber inferiorly. The intraocular gas bubble filled approximately 60% of the vitreous cavity. The retina was attached. A regimen of 250 mg of acetazolamide four times a day and timolol 0.5% twice a day was begun for intraocular pressure control. Prednisolone 1% hourly was also begun to prevent further fibrin formation. Nine hours later, intraocular pressure was 46 mm Hg. The anterior chamber was shallow centrally and closed for 360 degrees peripherally. Iris bombé was noted. The anterior chamber did not deepen with face-down positioning. At this time, 25 μg of tissue plasminogen activator was injected into the anterior chamber for fibrin pupillary

TABLE
CHARACTERISTICS OF PATIENTS RECEIVING TISSUE PLASMINOGEN ACTIVATOR INJECTION

PATIENT NO., AGE (YRS), SEX	PREOPERATIVE DIAGNOSIS	SURGICAL PROCEDURE	INTRAOCULAR PRESSURE (MM HG)		
			PREOPERATIVE	AT TIME OF INJECTION	72 HRS AFTER INJECTION
1, 50, M	Traumatic retinal detachment with proliferative vitreoretinopathy	Pars plana vitrectomy, scleral buckle, lensectomy, membrane stripping, fluid-gas exchange, with 20% C_3F_8, endolaser	1	46	25
2, 63, F	Proliferative vitreoretinopathy	Pars plana vitrectomy, lensectomy, membrane stripping, endolaser, fluid-gas exchange with 14% C_3F_8	13	32	17
3, 55, F	Traction retinal detachment secondary to proliferative vitreoretinopathy	Pars plana vitrectomy, lensectomy, endolaser, retinal membrane stripping, fluid-gas exchange with 20% C_3F_8	16	34	16
4, 65, M	Recurrent retinal detachment secondary to repair of giant tear	Fluid-gas exchange with 15% C_3F_8	15	46	7
5, 31, M	Traumatic retinal detachment with proliferative vitreoretinopathy	Pars plana vitrectomy, retinal membrane stripping, endolaser, fluid-gas exchange with 18% C_3F_8	10	22	14
6, 47, F	Recurrent rhegmatogenous retinal detachment with proliferative vitreoretinopathy	Pars plana vitrectomy, membrane stripping, endolaser, fluid-gas exchange with 14% C_3F_8	9	43	18
7, 31, M	Traction retinal detachment secondary to proliferative diabetic retinopathy	Pars plana vitrectomy, lensectomy, endolaser, membrane stripping, scleral buckle, fluid-gas exchange with 20% SF_6	18	42	22

block. Two hours 15 minutes later, the fibrin membrane had completely resolved. The intraocular pressure had decreased to 35 mm Hg. The inferior two thirds of the anterior chamber had markedly deepened. The superior one third of the anterior chamber remained shallow, but deepened with face-down positioning. Three days after injection, intraocular pressure was 25 mm Hg. The fibrin pupillary membrane did not reform.

Results

Tissue plasminogen activator, injected into the anterior chamber in five patients and intravitreally in two patients, resulted in lysis of the fibrin pupillary membrane within four hours after injection in all cases (Figure). The pupillary block mechanism was confirmed by rapid deepening of the anterior chamber as the fibrin began to dissolve, establishing free communication between the anterior and posterior chambers. In one patient (Patient 4), the anterior chamber was shallow one day after the injection, necessitating removal of additional gas and redeepening with sodium hyaluronate. Fibrin did not recur in this patient. Fibrin pupillary block recurred in Patient 3 eleven days after the initial injection of tissue plasminogen activator. After repeat injection, the pupillary block resolved, with no further fibrin recurrence.

No complications occurred in any patient as a result of tissue plasminogen activator injection. In particular, we did not encounter intraocular hemorrhage, infection, or corneal edema. In all

TABLE ***(Continued)***

INITIAL MANAGEMENT OF FIBRIN MEMBRANE	TIME TO RESOLUTION OF MEMBRANE (HRS)	SITE OF INJECTION	PREVIOUS VITRECTOMY	PREVIOUS SCLERAL BUCKLE
Prednisolone acetate 1% hourly	2¼	Anterior chamber	No	No
Prednisolone acetate 1% hourly	¾	Pars plana	No	Yes
Prednisolone acetate 1% hourly, argon laser membranolysis	4	Anterior chamber	Yes	Yes
Prednisolone acetate 1% hourly	½	Pars plana	Yes	Yes
None	1½	Anterior chamber	Yes	Yes
Prednisolone acetate 1% hourly, subconjunctival dexamethasone	2	Anterior chamber	Yes	Yes
Prednisolone acetate 1% hourly, 25 μg of tissue plasminogen activator	1	Anterior chamber	No	No

patients, the intraocular pressure returned to normal within three days after injection.

Discussion

Pupillary block caused by complete occlusion of the pupil by a fibrin membrane may occur in aphakic patients after vitreoretinal surgery with injection of intravitreal gas.[10,11] Increased intraocular pressure may result from iris bombé with closure of the anterior chamber angle.[12,13] Peripheral anterior synechiae form readily in these inflamed eyes, and iridocorneal adhesion may accompany shallowing of the anterior chamber caused by the iris bombé. Surgical and laser treatment modalities in the management of fibrin pupillary block have been described. Lewis, Han, and Williams[10] demonstrated the efficacy of argon laser lysis of fibrin pupillary membranes in the management of fibrin pupillary block glaucoma after vitrectomy surgery with intraocular gas injection. Michels[11] described surgical methods of creating an opening in the fibrin pupillary membrane. Argon laser treatment of fibrin pupillary membranes may be difficult in eyes with shallow or flat anterior chambers. Surgical manipulation in these eyes may be accompanied by an increase in inflammation, continued formation of fibrin, and closure of the opening in the fibrin membrane.

The results of our study suggest that tissue plasminogen activator is an effective means of treating fibrin pupillary block in patients who

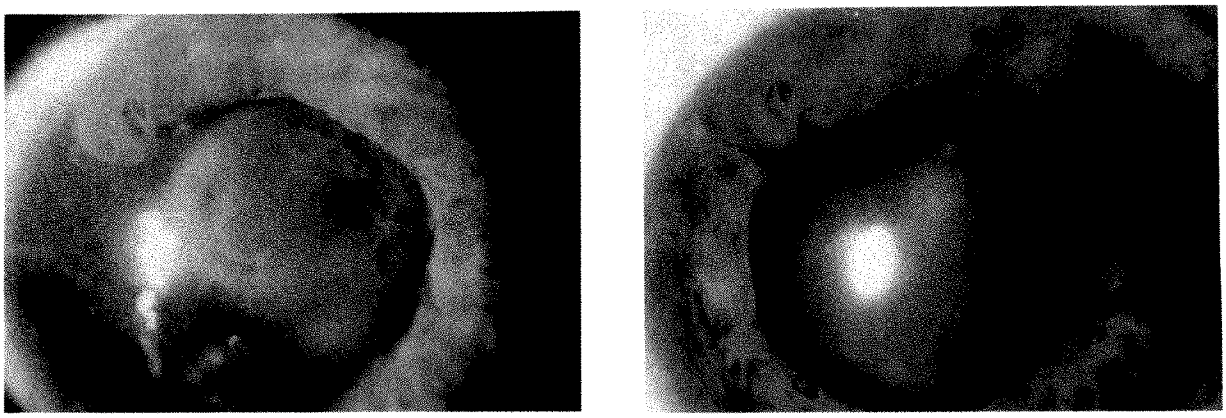

Figure (Jaffe and associates). Patient 7. Left, Before tissue plasminogen activator injection. Pupil is occluded by a complete fibrin membrane. Light directed from the temporal limbus has cast a crescentic shadow over the iris nasally as a result of iris bombé. Right, After tissue plasminogen activator injection. Fibrin membrane and pupillary block have completely resolved. Anterior chamber depth is normal.

develop severe fibrin formation after vitreoretinal surgery with intravitreal gas injection. Prompt treatment of the pupillary block may help to prevent the development of peripheral anterior synechiae. We also found that tissue plasminogen activator fibrinolysis was an effective adjunct in the management of the increased intraocular pressure that accompanied pupillary block in most patients. In patients with adequate anterior chamber depth, tissue plasminogen activator can be injected easily and safely via the corneoscleral limbus with minimal patient discomfort. In patients with iridocorneal apposition and a flat anterior chamber, injection through the pars plana may be required. In our study, the anterior chamber was sufficiently deep to permit anterior chamber injection by a limbal approach in five patients. In two patients, tissue plasminogen activator was injected into the vitreous cavity by a pars plana approach.

The dose used for treatment in the current study, 25 μg, was chosen on the basis of its efficacy, lack of ocular toxicity, and pharmacokinetics in experimental animal studies of intravitreal fibrinolysis.[4,14] It was also identical to that used in previous studies of the use of tissue plasminogen activator in the treatment of postvitrectomy fibrin formation[1] and filtering bleb thrombolysis.[2] This dose is sevenfold higher than one found to be effective in the treatment of anterior chamber fibrin in a rabbit model.[3] In that model, the anterior chamber and vitreous cavity were separated by the crystalline lens. In the current study, free communication between the anterior chamber and vitreous cavity was similarly prevented by the presence of the fibrin pupillary membrane. Because of rapid fibrinolysis, however, tissue plasminogen activator injected into the anterior chamber quickly communicated with the vitreous cavity. Although we encountered no complications from tissue plasminogen activator injection in these seven patients, potential risks of such an intraocular injection, including hemorrhage and infection, should be discussed with the patient.

Intraocular tissue plasminogen activator injection may be considered in the initial treatment of patients with fibrin pupillary block after vitreous surgery. Short-term results of this treatment modality are encouraging. Longer patient follow-up and further experience in the treatment of additional patients will be necessary to document fully the efficacy and safety of this form of treatment.

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Ophthalmic miniature

It took five years to kill him, and he stood it well. If ever he had been a little irregular he atoned for it in that long martyrdom. He kept an admirable record of his own symptoms, and worked out the eye changes more fully than has ever been done. When the ptosis got very bad he would hold up his eyelid with one hand while he wrote. Then, when he could not co-ordinate his muscles to write, he dictated to his nurse. So died, in the odour of science, James Walker, aet. 45.

Arthur Conan Doyle, *The Surgeon Talks*

Fibrovascular Proliferation and Retinal Detachment After Intravitreal Injection of Activated Macrophages in the Rabbit Eye

Yan-Nian Hui, M.D., Randi Goodnight, B.Sc., Nino Sorgente, Ph.D., and Stephen J. Ryan, M.D.

Injection of activated macrophages into the posterior vitreous of the rabbit induced vigorous fibrovascular proliferation over the optic disk and medullary rays, as demontrated by ^{3}H-thymidine autoradiography. One week after injection, endothelial cells and pericytes of the capillaries near the inner surface of the optic disk and rays were labeled; fibroblast-like cells, which were also labeled, migrated and formed vitreous strands. By the second week after injection, the fibrovascular tissue proliferated most actively, and traction medullary ray detachment and peripapillary retinal fold formation were observed. The cellular proliferation was accompanied by inflammatory cell infiltration. Glial cells within the optic disk, as well as retinal pigment epithelial cells beneath the detached retina, were labeled by ^{3}H-thymidine. These results demonstrate that the fibrovascular proliferation originates from the vessel complex of the optic disk and medullary rays in this experimental model of retinal detachment.

FIBROBLASTS are one of the main cellular components of the vitreous strands and epiretinal membranes[1-6] that lead to traction retinal detachment.[7] The origin of the fibroblasts remains unknown,[5] although in experimental posterior penetrating ocular injury, fibroblastic proliferation into the vitreous was observed to originate from the wound as well as from the optic nerve head. Presumably fibroblastic proliferation can originate from retinal vessels, or even mesenchymal sources within the optic nerve or choroid,[1,4,5] but this has not been proven.

Cleary and Ryan[8] established a rabbit model that is suitable for further study of cellular proliferation and retinal detachment. In our model, fibrous proliferation and medullary ray detachment are induced by intravitreal injection of activated macrophages, rather than by injection of cultured fibroblasts. We found evidence that fibroblasts within the vitreous strands originate from the vascular tissue of the optic disk and medullary rays.

Material and Methods

Animal model—We used 30 pigmented rabbits of either sex weighing 2 to 3 kg, in accordance with the Association for Research in Vision and Ophthalmology Resolution on the Use of Animals in Research. As previously described,[9] activated macrophages were collected from the peritoneal cavity of rabbits four days after intraperitoneal injection of 15 ml of 3% thioglycolate medium. The cells were suspended in RPMI 1640 medium, supplemented with 5% heat-inactivated fetal bovine serum at a concentration of 6 to 8 × 10^{6} cells/ml, and used immediately. For intravitreal injection of macrophages, the animals were anesthetized with an intramuscular injection of a 3:1:1 mixture of ketamine hydrochloride, acepromazine maleate, and atropine sulfate; pupils were dilated with one drop of 10% phenylephrine hydrochloride, 1% tropicamide, and 1% atropine sulfate. Under direct visualization with an operating microscope, the right eye of each rabbit was injected with 0.1 ml of activated macrophage suspension, using a 27-gauge needle inserted through the pars plana into the posterior vitreous cavity.

The eyes were examined twice each week

Accepted for publication May 5, 1989.
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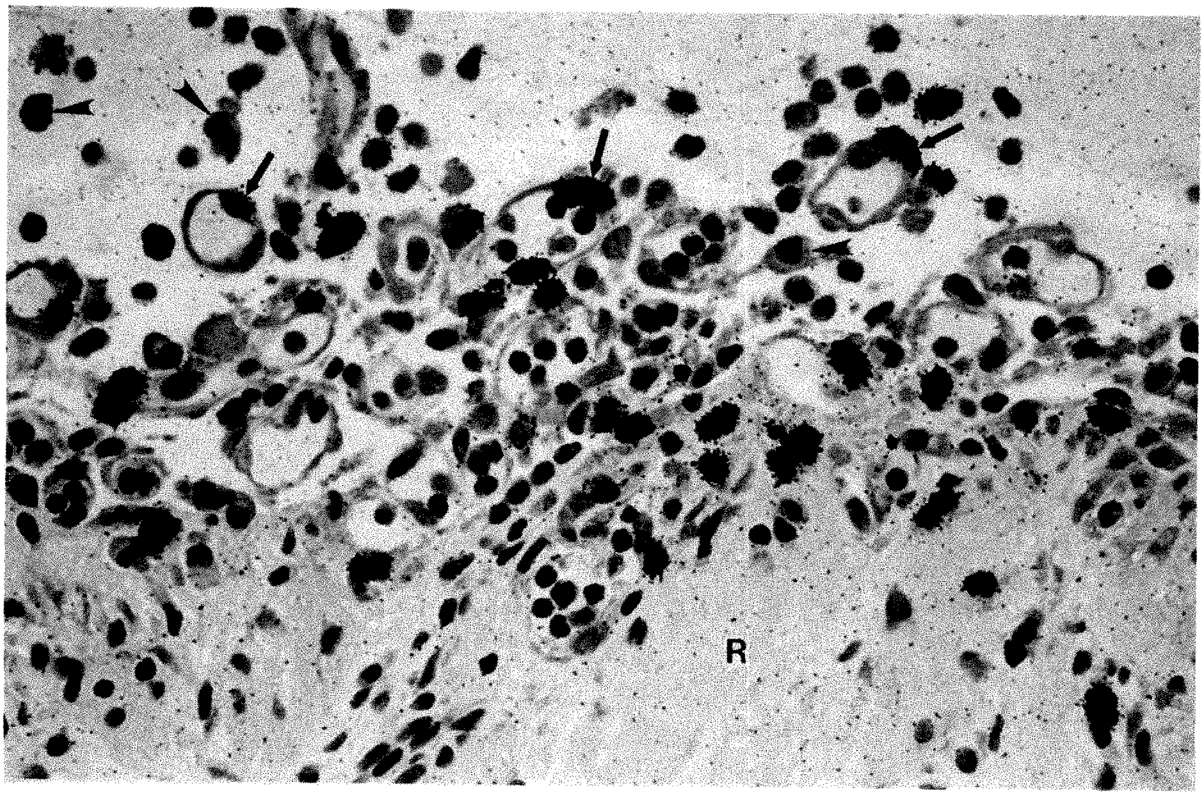

Fig. 1 (Hui and associates). Fibrovascular proliferation at the inner surface of the optic disk (R) one week after macrophage injection. Note the labeled nuclei (arrows) of capillary endothelial cells and pericytes. Macrophages (arrowheads) and other inflammatory cells infiltrate this area (hematoxylin and eosin, ×100).

with an indirect ophthalmoscope to document the formation of and to follow-up vitreous strands and evidence of traction and retinal detachment. Six animals were killed at each interval of seven, ten, 14, 21, and 28 days after macrophage injection.

Autoradiography—Autoradiography was done on four rabbits at each of the designated times. Twenty hours before they were to be killed, 100 μCi of tritiated thymidine in 0.1 ml of balanced saline solution was injected into the vitreous cavity of the right eye. At the end of the incubation, the eyes were enucleated and the corneas were removed. The eyes were fixed in 2% paraformaldehyde and 2.5% glutaraldehyde in phosphate buffer, pH 7.4, for 24 hours. The eyes were then examined under a dissecting microscope; tissue blocks, including the vitreous strand, optic disk, and the medullary rays, were dissected, rinsed, dehydrated in a series of graded alcohols, and embedded in glycol methacrylate. Using a microtome, 3-μm sections were cut; these were dipped into Kodak NTB-2 nuclear emulsion diluted 1:1 with water and heated to 42 C under safe-light conditions. The slides were allowed to dry and packed into light-tight boxes with desiccant. After one week exposure at 4 C, the slides were developed in Kodak D-19 developer at 20 C for three minutes, rinsed, and fixed in Kodak Rapid Fix for three minutes. After extensive rinsing, the sections were stained with hematoxylin and eosin and coverslipped. To compare the proliferation rates at different intervals after macrophage injection, labeled cell nuclei in the proliferating membranes were counted in three to five ×40 fields from each section.

At each time period, two additional animals were killed and the eyes used for conventional light microscopy and transmission electron microscopy. Specimens of the vitreous strand, optic disk, and medullary rays were stained with Alcian blue, postfixed in 2% buffered osmium, dehydrated in a graded series of alcohol, and embedded in plastic. Ultrathin sections were stained with lead citrate and uranyl acetate, and examined and photographed with an electron microscope.

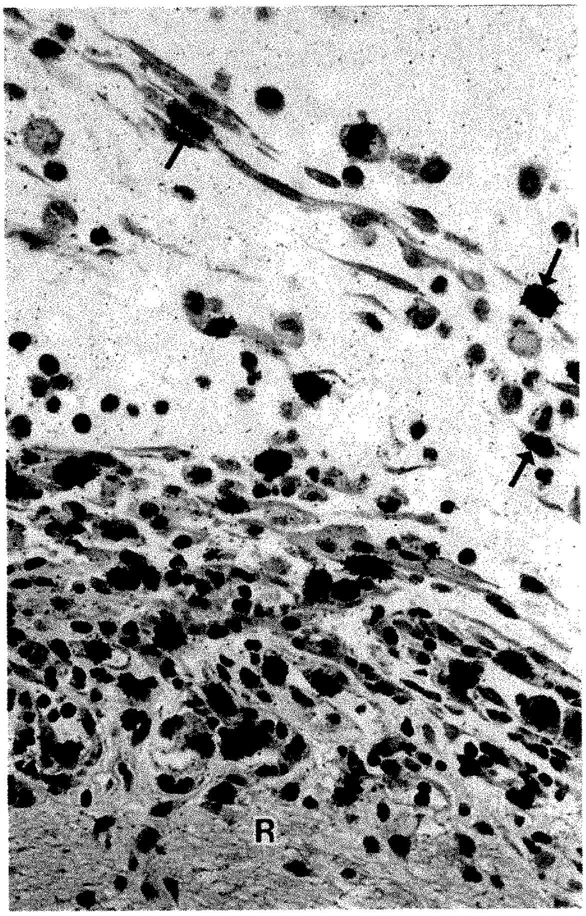

Fig. 2 (Hui and associates). Light micrograph showing fibrovascular proliferation one week after injection. Fibroblast-like cells, some of which have labeled nuclei (arrows), are round or spindle-shaped and appear to migrate and to line up. R, optic disk (hematoxylin and eosin, ×100).

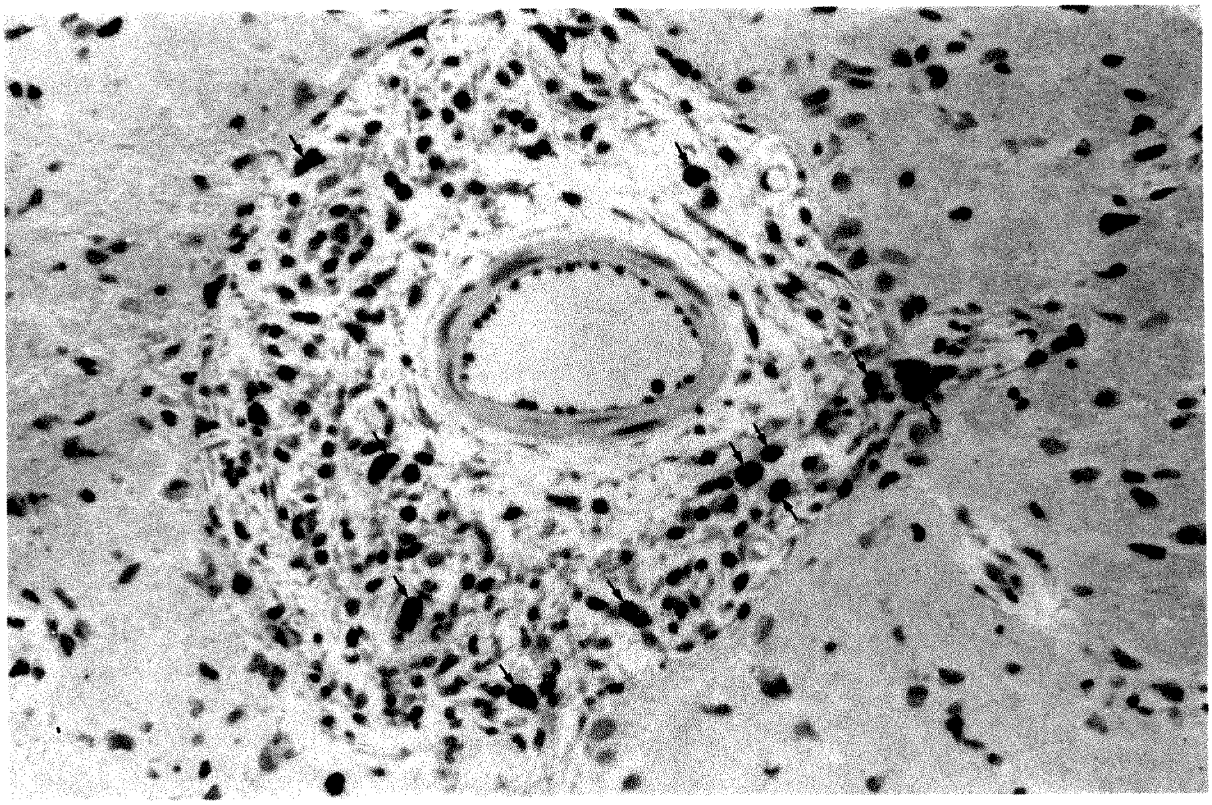

Fig. 3 (Hui and associates). Fibroblast-like cells and capillaries proliferate in the vascular complex deep in the optic disk one week after injection. Note the labeled nuclei (arrows) and a small artery in the center of the complex (hematoxylin and eosin, ×65).

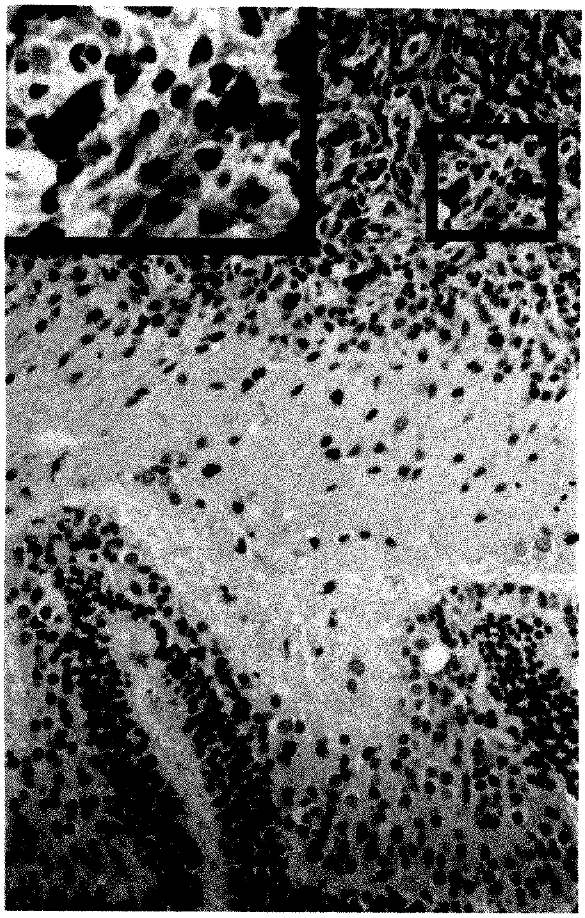

Fig. 4 (Hui and associates). Vigorous fibrovascular proliferation and traction detachment of the medullary rays adjacent to the optic disk two weeks after injection (hematoxylin and eosin, ×200). Many cell nuclei are labeled (inset, hematoxylin and eosin, ×800).

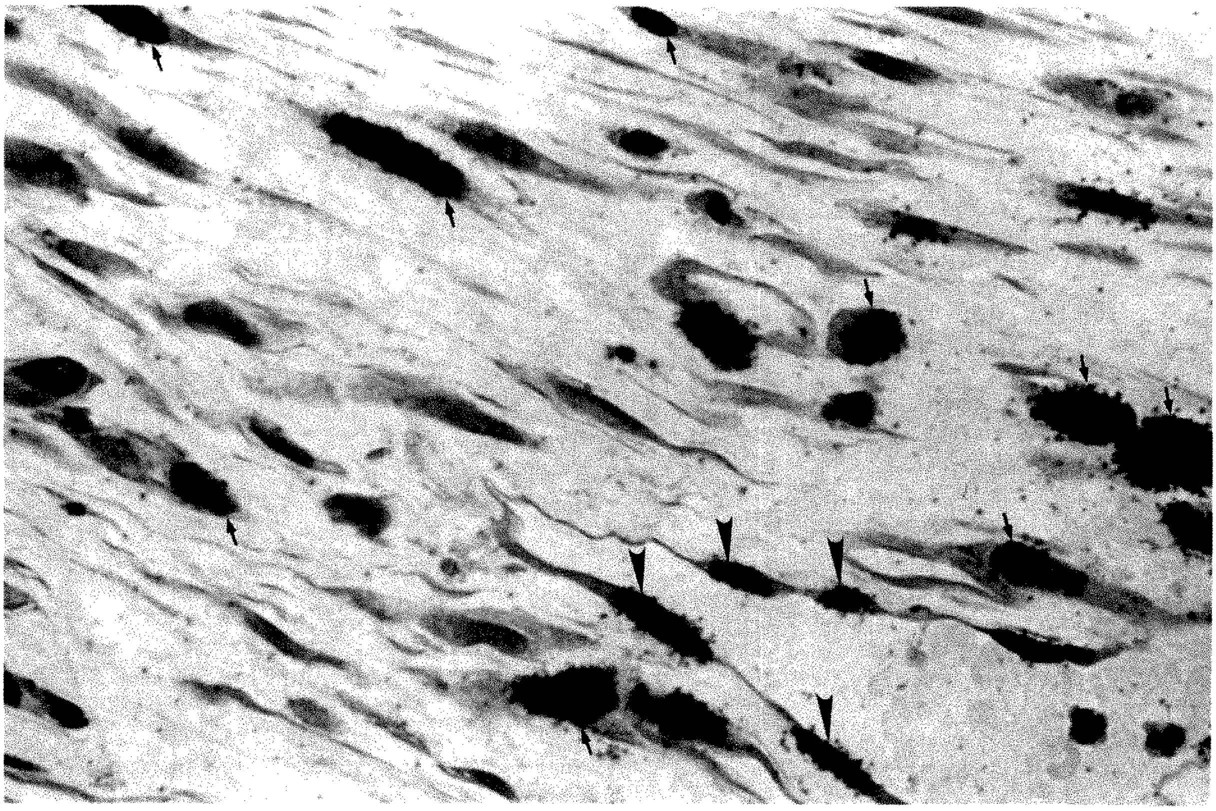

Fig. 5 (Hui and associates). Fibroblastic proliferation in the vitreous strand two weeks after injection. Note the labeled nuclei (arrows) and macrophages (arrowheads), but no capillary in this area (hematoxylin and eosin, ×100).

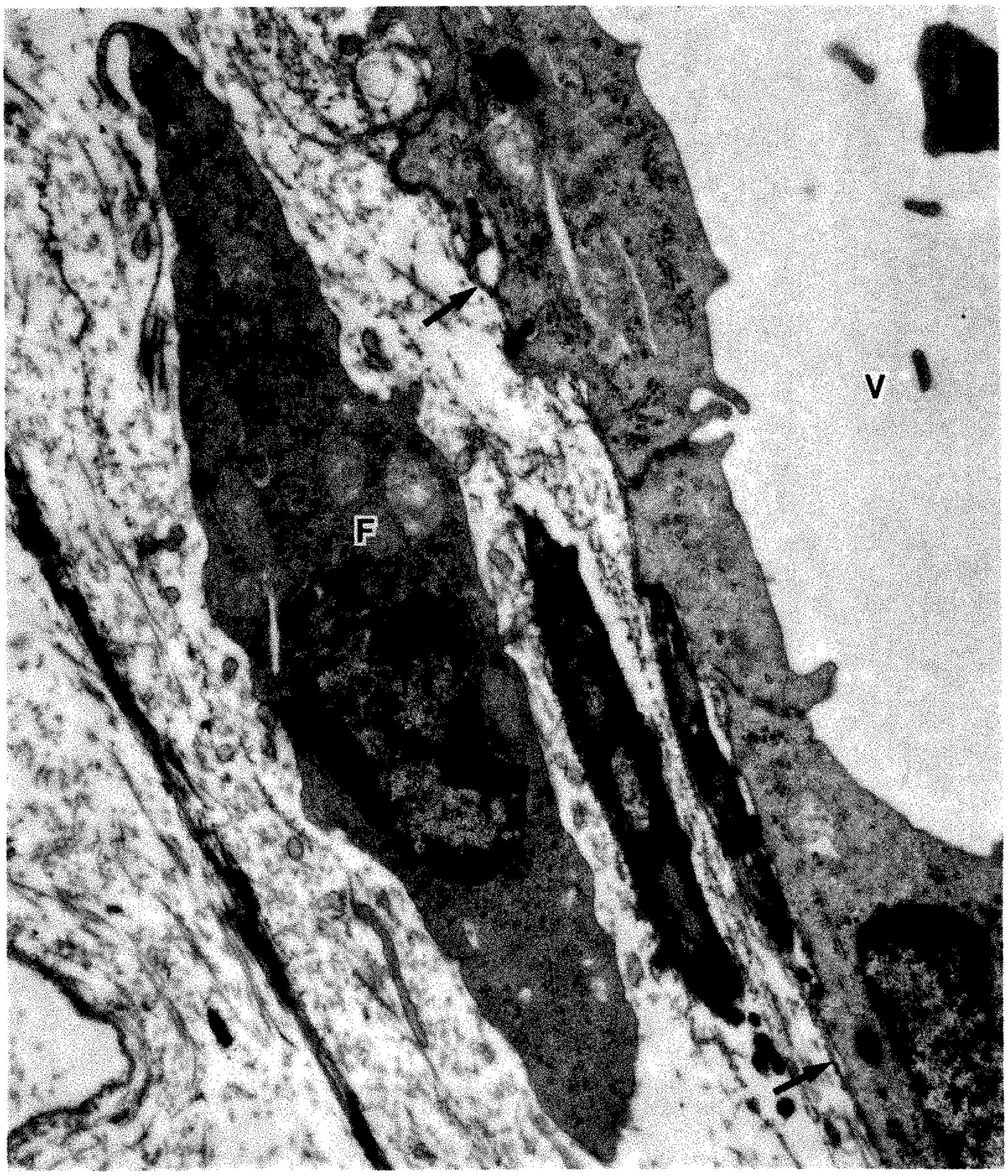

Fig. 6 (Hui and associates). One week after injection a fibroblast-like cell (F) is present close to a large capillary (V), but it is not enveloped in the basement membrane (arrows). Note the cell with few microvillous projections and with collagenous fibrils around it (transmission electron micrograph, ×6,300).

Results

One day after macrophage injection a white strand was visible in the posterior vitreous. By the first week the strand approached the optic disk and medullary rays, the vitreous over the optic disk became cloudy, the optic disk showed hyperemia, and vessels over the disk and medullary rays were dilated and tortuous. As seen by light microscopy, the internal surface of the optic disk contained an increased number of capillaries, as well as spindle-shaped cells and inflammatory cell infiltration. In some capillaries the nuclei of endothelial cells and pericytes were labeled (Fig. 1). The

TABLE
REPRODUCTION ACTIVITY DETERMINED BY AUTORADIOGRAPHY

DURATION AFTER INJECTION	NO. OF EYES	MEAN ± S.D. COUNTS OF LABELED NUCLEI PER UNIT AREA
7 days	4	80.2 ± 7.4
10 days	4	117.3 ± 12.8
14 days	4	187.3 ± 18.8
3 wks	4	65.4 ± 7.2
4 wks	4	26.1 ± 5.4

spindle-shaped cells showed fibroblastic features with round or oval nuclei, some of which became labeled; these fibroblast-like cells appeared to migrate away from the internal surface of the optic disk and to assume a linear arrangement in the vitreous (Fig. 2). Most inflammatory cells were macrophages with abundant cytoplasm and oval or kidney-shaped nuclei. Besides the proliferating capillaries and fibroblast-like cells at the inner surface of the optic disk and medullary rays, a number of nuclei of endothelial cells and of fibroblast-like cells in vessel complexes in the optic disk were also labeled (Fig. 3); a few labeled retinal pigment epithelial cells in situ and rare labeled endothelial cells of capillaries of the choroid were observed immediately adjacent to the optic disk.

During the second week the vitreous strand became attached to the optic disk and medullary rays, which became elevated. Of 12 eyes, nine had localized medullary ray detachment with peripapillary retinal folds.

By light microscopy the vitreous strand attached to the optic disk showed active cellular proliferation; the mean ± S.D. count of labeled cell nuclei per field reached a peak of 187.3 ± 18.8 (Table). Numerous fibroblast-like cells and capillary endothelial cells in the proliferating tissue adjacent to the optic disk were crowded with inflammatory cells; many of these cells had labeled nuclei and the retina in this area showed folds and focal detachment (Fig. 4). There was vigorous fibroblastic proliferation in the vitreous strand, extending about 1.5 to 2 mm from the optic disk (Fig. 5).

By the third week after injection, all eight eyes had localized detachment of the medullary rays with peripapillary retinal folds. The mean count of labeled cell nuclei per unit area in the proliferating tissue decreased to an average of 65.4 ± 7.2.

During the fourth week the retinal detachment remained stable and, remarkably, the inflammatory cell infiltration lessened in the vitreous and near the optic disk and medullary rays. In the vitreous strand, nuclei of several fibroblasts were still labeled and a few capillaries near the optic disk contained endothelial cells or pericytes with labeled nuclei. Limited glial proliferation with labeled nuclei was also observed on the inner surface of the optic disk; this glial proliferation formed an epiretinal membrane with tissue bridges connecting the membrane and the retina proper. Subretinal membranes with labeled cell nuclei developed locally beneath the detached retina; at the initiation of retinal detachment, retinal pigment epithelial cells with labeled nuclei migrated into the subretinal space.

Transmission electron microscopy showed the spindle-shaped cells in the vitreous strands to have characteristics typical of fibroblasts, including rough endoplasmic reticulum, mitochondria, and a number of microfilaments. These cells lacked polarization with respect to apical processes or basement membrane and lacked defined cell junctions. Some fibroblast-like cells were in close proximity to large capillaries; these cells were separated from the capillary wall and were not enveloped in the basement membrane of the vessel (Fig. 6). Newly formed capillaries were also seen adjacent to the optic disk (Fig. 7).

Discussion

In this study, only macrophages were introduced into the vitreous of rabbits. Unlike a number of other cell types, such as cultured fibroblasts,[10-12] retinal pigment epithelial cells,[13] retinal Müller cells,[14] and even chondrocytes,[15] all of which have been shown to proliferate in the vitreous, macrophages do not transform into fibroblast-like cells[16] and do not proliferate. Our injection through the pars plana induced only minimal wound repair. Thus, intravitreal fibrovascular proliferation in this model must have originated from the ocular tissue rather than from injected cells. This confirms a previous experiment, using prelabeled fibroblasts, that resulted in vitreous membranes composed of few labeled cells, indicating the ocular origin

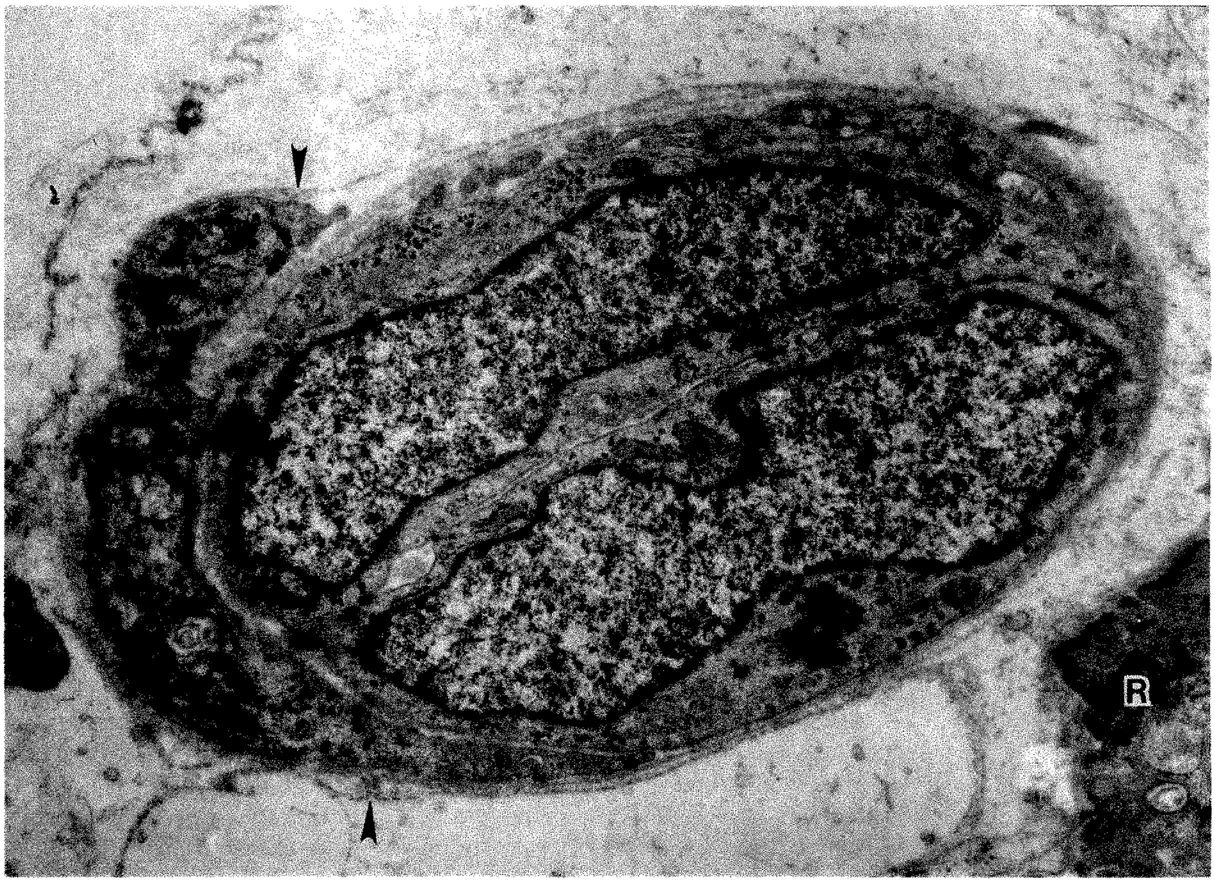

Fig. 7 (Hui and associates). A newly formed capillary is present close to the optic disk (R). Note the slit-like lumen (open arrow) and junctional zones (arrows between endothelial cells). Portions of pericytes are enveloped by the basement membrane-like substance (arrowheads) (transmission electron micrograph, ×6,300).

of the proliferating tissue.[9] That macrophages play an important role in initiating migration and proliferation of cells in the vitreous has been previously suggested by Algvere and Martini.[17] Their intravitreal injections of carbon particles in monkeys caused fibrovascular strands in the vitreous and subsequent retinal detachments. In their studies, the proliferation could have originated only from the ocular tissue.

After an intravitreal injection of cultured fibroblasts, an earlier study showed that neovascularization occurred only when the injected fibroblasts came into direct contact with the vascular complex of the rabbit eye.[18] Using tritiated thymidine autoradiography in conjunction with transmission electron microscopy, we also demonstrated that the fibrovascular proliferation originated from the vascular tissue of the optic disk and medullary rays. Many small vessels at these sites had labeled nuclei, indicating that their cells were undergoing DNA synthesis. Newly formed capillaries are composed of endothelial cells and their accompanying pericytes. Although it is difficult to identify proliferating endothelial cells and pericytes by autoradiography, these two types of cells can be discerned by transmission electron microscopy. Both cell types are rich in cytoplasmic organelles and are enmeshed in the basement membrane of the vessel. Endothelial cells have junctional complexes with adjacent endothelial cells, and are associated with vascular lumen. Pericytes are identified on the basis of their juxtaendothelial position, the presence of basement membrane-like materials, and lack of direct association with the vascular lumen.[19,20]

We observed fibroblasts constituting the main portion of the vitreous strands. These cells could originate from mesenchymal cells of the vessel complexes, as it has been suggested that mesenchymal cells are involved in normal retinal vascularization.[21] Crocker, Murad, and Geer[22] demonstrated perivascular primitive mesenchymal cells in wound healing experi-

ments; these cells appear to differentiate into fibroblasts and are characterized by undifferentiated cytoplasm, a poorly developed granular endoplasmic reticulum, and absence of basement membrane. We assume that the fibroblast-like cells adjacent to vessels (Fig. 6) are mesenchymal cells that have undergone differentiation into fibroblasts, since they appear to meet some of the ultrastructural criteria, such as abundance of free ribosomes and lack of basement membrane.[19,22] We believe these cells to be fibroblasts because (1) they are not endothelial cells or pericytes based on their ultrastructure; (2) they do not have any features of glial cells[23] or of retinal pigment epithelial cells, such as intermediate filaments, polarization, or pigment; and (3) typical fibroblasts are present in the vitreous strand.

In addition to the vascular tissue, glial and retinal pigment epithelial cells could contribute to the cellular elements in the vitreous.[5,6] We did observe glial proliferation from the retina; this proliferation formed epiretinal membranes, but these did not contribute to the vitreous strands since no retinal tear occurred.[6] Our morphologic examination also confirmed that no cells with characteristics of glial or retinal pigment epithelial cells were present in the vitreous strands.

In these experiments, even though the count of labeled cell nuclei per field may not accurately represent the rate of proliferation, the count does show that the maximum value was reached ten to 14 days after macrophage injection, coinciding with the time at which localized medullary ray detachment occurred. These results lend support to the hypothesis that a critical mass of viable cells is necessary for the development of a traction retinal detachment.[20]

ACKNOWLEDGMENT

The animals used in this study were maintained in animal care facilities fully accredited by the American Association of Laboratory Animal Science.

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Ophthalmic miniature

Why are they beautiful? Certainly not for the pleasure of man, as Darwin's opponents claimed: butterflies existed at least one hundred million years before the first man. I believe that our very concept of beauty, necessarily relative and cultural, has over the centuries patterned itself on them, as on the stars, the mountains, and the sea. We have proof of this if we consider what happens when we examine the head of a butterfly under the microscope; for the greater number of observers, admiration is replaced by horror or revulsion. Not being culturally accustomed to it, we find this new object disconcerting; the enormous eyes without pupils, the horn-like antennae, the monstrous, juglike mouth, look to us like a diabolical mask, a distorted parody of the human face.

Primo Levi, *Other People's Trades*
New York, Summit Books, 1989, p. 17

Decreasing Frequency of Enucleation in Patients With Retinoblastoma

Jerry A. Shields, M.D., Carol L. Shields, M.D., and Varunan Sivalingam, M.D.

We reviewed our 15-year experience with the management of 324 cases of retinoblastoma. There has been a definite trend away from enucleation in both unilateral and bilateral cases during recent years. In cases of unilateral retinoblastoma, the affected eye was salvaged in 4% of cases (two of 49) during the five-year interval from 1974 through 1978, in 14% of cases (seven of 50) from 1979 through 1983, and in 25% of cases (20 of 80) from 1984 through 1988. In cases of bilateral retinoblastoma, both affected eyes were salvaged in 4% of cases (one of 24) from 1974 through 1978, in 18% of cases (nine of 50) from 1979 through 1983, and in 25% of cases (18 of 71) from 1984 through 1988. Earlier diagnosis of retinoblastoma and refinements in conservative methods of management are believed to be the main reasons for this trend away from enucleation.

THE CONVENTIONAL TREATMENT for unilateral retinoblastoma has been enucleation of the affected eye. The standard treatment for bilateral retinoblastoma has been enucleation of the more severely affected eye and treatment of the less affected eye by radiotherapy, photocoagulation, cryotherapy, or combinations of these conservative methods.[1-4] Although enucleation still remains an acceptable method of treatment, we have been able to salvage more affected eyes in recent years by using these conservative modalities.[2-5] We reviewed our experience on the Ocular Oncology Service at our institution in the treatment of 324 patients with retinoblastoma during the 15-year interval between Jan. 1, 1974, and Dec. 31, 1988, to determine the frequency with which enucleation has been performed. The purpose of this study was to determine and to document a possible trend away from enucleation in recent years.

Patients and Methods

Prospective data have been collected since early 1974 on all patients with retinoblastoma who were referred to the Ocular Oncology Service at our institution. The method of treatment used in each case was based on the size, extent, and location of the tumors. The relative indications for the various therapeutic modalities have been described elsewhere.[2-5] Although the indications have gradually changed over the course of this study, enucleation was generally advised when more than 50% of the retina was affected by the tumor or when an ophthalmoscopic view of the optic nerve was obscured by a large tumor. Macular involvement by relatively smaller tumors was not necessarily an indication for enucleation in either unilateral or bilateral cases.

In children with unilateral disease, we reviewed the number and percent who required enucleation each year and then calculated the percent in which we were able to salvage the affected eye. In children with bilateral disease, we determined the percent who required enucleation of one eye, the percent who required enucleation of both eyes, and the percent in whom we were able to salvage both eyes.

Accepted for publication May 12, 1989.

From the Ocular Oncology Service, Wills Eye Hospital, Jefferson Medical College, Thomas Jefferson University, Philadelphia. This study was supported in part by the Ocular Oncology Fund and the Oncology Research Fund, Wills Eye Hospital, and in part by the Black Patch Invitational Golf Tournament, Downingtown, Pennsylvania.

Reprint requests to Jerry A. Shields, M.D., Director, Ocular Oncology Service, Wills Eye Hospital, Ninth and Walnut Streets, Philadelphia, PA 19107.

Results

A total of 324 patients with retinoblastoma were treated during the 15-year period between January 1974 and December 1988. There were 179 children with unilateral retinoblastoma and 145 with bilateral disease.

A review of the unilateral cases showed a gradual but definite trend away from enucleation of the affected eye (Table 1). Further analysis showed that the affected eye was salvaged in 4% of cases (two of 49) during the years 1974 to 1978, in 14% of cases (seven of 50) during the years 1979 to 1983, and in 25% of cases (20 of 80) during the years 1984 to 1988 (Table 2). In 1988 the affected eye was treated conservatively in 35% of cases (seven of 20) as compared to 0% (zero of six) in 1974 (Table 1). In general, the tumor in most of the children treated conservatively was diagnosed relatively early and much of the retina was uninvolved.

Review of the bilateral cases also showed a similar trend away from enucleation (Table 3). Both eyes were salvaged in 4% of cases (one of 24) during the first five years, in 18% of cases (nine of 50) during the second five years, and in 25% (18 of 71) in the last five years (Table 4). Of the 145 patients with bilateral disease, 97 (67%) underwent enucleation of one eye, 20 (14%) had enucleation of both eyes, and 28 (19%) did not require enucleation of either eye. Of the 20 patients treated with bilateral enucleation, one had primary bilateral enucleation and 19 ultimately underwent enucleation of the remaining contralateral eye after attempts at conservative treatment had failed. In general, the cases of bilateral enucleation were characterized by very advanced bilateral involvement at the time of initial diagnosis.

TABLE 1
CHANGING TRENDS IN THE MANAGEMENT OF UNILATERAL RETINOBLASTOMA

YEAR	TOTAL NO. OF CASES*	NO. OF UNILATERAL CASES	NO. (%) OF EYES ENUCLEATED IN UNILATERAL CASES	% SALVAGE OF AFFECTED EYE
1974	7	6	6 (100)	0
1975	13	7	6 (86)	14
1976	18	15	15 (100)	0
1977	15	13	13 (100)	0
1978	20	8	7 (88)	12
1979	19	9	8 (89)	11
1980	22	10	9 (90)	10
1981	18	9	8 (89)	11
1982	16	10	8 (80)	20
1983	25	12	10 (83)	17
1984	28	17	13 (76)	24
1985	42	23	17 (74)	16
1986	24	8	6 (75)	25
1987	25	12	11 (92)	8
1988	32	20	13 (65)	35
Total	324	179	150 (84)	16

*Includes unilateral and bilateral cases.

TABLE 2
SALVAGE RATES OF AFFECTED EYE IN CHILDREN WITH UNILATERAL RETINOBLASTOMA

5-YEAR INTERVAL	TOTAL NO. OF UNILATERAL CASES	NO. (%) NOT ENUCLEATED
1974–1978	49	2 (4)
1979–1983	50	7 (14)
1984–1988	80	20 (25)
Total	179	29 (16)

Discussion

This study clearly demonstrated a trend away from enucleation in children with retinoblastoma referred to an ocular oncology center for treatment. There are several apparent reasons for this trend. First, many ophthalmologists, pediatricians, and optometrists are becoming more aware of the signs and symptoms of retinoblastoma and tend to make a diagnosis earlier when the tumors are at a stage where conservative treatment is a feasible option. In some cases karyotype studies performed by pediatricians for a variety of reasons have demonstrated a deletion in the long arm of chromosome 13, which has prompted referral to ophthalmologists who made the diagnosis of retinoblastoma at a very early stage.[6] Second, there have been refinements in conservative methods of treatment. Improved delivery systems for photocoagulation and cryotherapy are now available. Newer techniques in radioactive plaque brachytherapy are also available.[5] Finally, our continued experience with photocoagulation, cryotherapy, and radiotherapeutic methods have enabled us to understand better the indications and limitations of these techniques.[4,5]

Some of our more recently treated children

TABLE 3
CHANGING TRENDS IN THE MANAGEMENT OF BILATERAL RETINOBLASTOMA

YEAR	TOTAL NO. OF CASES*	TOTAL NO. OF BILATERAL CASES	NO. (%) REQUIRING ENUCLEATION OF BOTH EYES	NO. (%) REQUIRING ENUCLEATION OF ONE EYE	NO. (%) NOT REQUIRING ENUCLEATION
1974	7	1	0 (0)	1 (100)	0 (0)
1975	13	6	1 (17)	5 (83)	0 (0)
1976	18	3	3 (100)	0 (0)	0 (0)
1977	15	2	0 (0)	2 (100)	0 (0)
1978	20	12	3 (25)	8 (67)	1 (8)
1979	19	10	5 (50)	5 (50)	0 (0)
1980	22	12	0 (0)	9 (75)	3 (25)
1981	18	9	0 (0)	9 (100)	0 (0)
1982	16	6	0 (0)	5 (83)	1 (17)
1983	25	13	1 (8)	7 (54)	5 (38)
1984	28	11	3 (27)	7 (64)	1 (9)
1985	42	19	1 (5)	13 (68)	5 (26)
1986	24	16	2 (13)	10 (63)	4 (25)
1987	25	13	1 (8)	8 (62)	4 (31)
1988	32	12	0 (0)	8 (67)	4 (33)
Total	324	145	20 (14)	97 (67)	28 (19)

*Includes unilateral and bilateral cases.

may ultimately require enucleation of the affected eye if the currently used treatment should fail. In most cases that required enucleation after treatment failure, however, removal of the eye was necessary within a few months after treatment. Therefore, we believe that the overall trend away from enucleation will not be significantly altered by such occasional occurrences.

The most important question regarding the use of alternative methods of treatment for retinoblastoma relates to whether the mortality rate is adversely affected by the use of such methods. Since many patients receive multiple treatment modalities, depending upon the overall clinical findings, a precise comparison becomes extremely difficult. However, our recent experience suggests that there is approximately a 5% chance of metastatic retinoblastoma in patients treated by enucleation and in patients treated conservatively. We currently believe that conservative methods do not adversely affect the systemic prognosis.

A second important question regarding conservative treatment of retinoblastoma relates to whether useful vision is retained in the treated eyes. Our unpublished data on visual results in eyes treated with photocoagulation, cryotherapy, or radiotherapy indicates that useful vision is retained and the eye remains comfortable in almost all cases. We generally recommend enucleation, rather than conservative methods, if our initial clinical evaluation suggests that there is no appreciable hope for retention of some sight in the affected eye.

Despite this gradual trend away from enucleation at a major ocular oncology referral center, it should be stressed that most cases of retinoblastoma are still managed by enucleation. Enucleation is an appropriate method of management for most children with unilateral sporadic disease and it is an acceptable method for treating the most advanced eye in most bilateral cases. Early enucleation is generally believed to have been responsible for saving the lives of many children and it still remains the most widely used therapeutic option. Many clinicians choose to advise enucleation in most cases and we have no reason to disagree with their opinion in that regard. However, we have hopes that with earlier detection of retinoblastoma and continued improvements in conservative methods of treatment more children will be treated conservatively and will enjoy the benefit of having some vision in the affected eye without an adverse affect on their systemic prognosis.

TABLE 4
SALVAGE RATES OF ONE OR BOTH EYES IN CHILDREN WITH BILATERAL RETINOBLASTOMA

5-YEAR INTERVAL	TOTAL NO. OF BILATERAL CASES	NO. (%) REQUIRING ENUCLEATION OF BOTH EYES	NO. (%) REQUIRING ENUCLEATION OF ONE EYE	NO. (%) NOT REQUIRING ENUCLEATION
1974–1978	24	7 (29)	16 (67)	1 (4)
1979–1983	50	6 (12)	35 (70)	9 (18)
1984–1988	71	7 (10)	46 (65)	18 (25)
Total	145	20 (14)	97 (67)	28 (19)

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AMERICAN JOURNAL OF OPHTHALMOLOGY®

FRANK W. NEWELL, *Publisher and Editor-in-Chief*
Suite 1415, 435 North Michigan Ave., Chicago, Illinois 60611

Published monthly by the OPHTHALMIC PUBLISHING COMPANY
Suite 1415, 435 North Michigan Avenue, Chicago, Illinois 60611

EDITORIAL

Interpreting Automated Perimetry

Douglas R. Anderson

The computer now helps us with perimetry, but only in part. A technician must still run the test, keep the patient optimally attentive to the task, instruct the patient when, for example, they are too quick to give false-positive responses, and monitor that all technical details are in order—that the corrective lens is centered, the patient's head remains in position, and so on. Thus, the computerized perimeter helps the technician do the task but does not take over the job of administering the field examination.

See also p. 130.

Similarly, the computer does not take over the ophthalmologist's job of interpreting the results. Just as was true of manual perimetry, the physician must use experienced judgment to decide whether any of the findings are abnormal, whether a certain abnormal finding is an artifact or is indicative of disease (of which other signs may be present), or whether a new field examination represents a change from the previous state.

The physician will always have to use professional judgment for interpretation, but, the computer can help. The computer can perform both simple and complex arithmetic computations, providing assistance with some helpful quantitative information ("reliability" scores, duplicate values for suspicious points, subtractions from normal values-for-age, global indices such as the mean deviation, and the like). Most of the present statistical calculations have to do with whether or not a given field examination is abnormal. There is less mathematical help (and hence a more difficult task for the physician) in deciding whether a field has changed on follow-up examination; only primitive statistical help is presently available for this problem.

In this issue of THE JOURNAL, Heijl, Lindgren, and Lindgren take us further into the use of

numeric computation to assist with interpreting progressive change in the visual field. They determined point-by-point variation of threshold value upon repeat testing (which includes both so-called short-term and long-term fluctuations) for static threshold testing in the central 30 degrees with the Humphrey perimeter. Three main concepts can be gleaned from the detailed statistics.

First, if a normal threshold sensitivity value is present on the first field at some point, and if a field test is unchanged, the variation is less near the center (less than a 6- to 8-dB deterioration 95% of the time) than it is near the edge of the 30-degree central field (up to 15 dB to reach the 95th percentile).

Second, if the threshold value is depressed by 10 dB or more on the first test, there may be by chance alone a zero sensitivity value on the second test, even if there is no progression.

Third, because there is such a wide range of variation at a single point on duplicate examination (and, especially if there is a relative defect already present on the first field), it is difficult to document progression by one pair of field examinations performed several months or a year apart. It is better to have a baseline average of, say, two or even three field examinations. Then on follow-up, if there is suspicion of change, a second follow-up field might be able to confirm that a small change is real.

Although the present study immediately provides us with this guidance in interpretation, the detailed data will also provide a basis for more sophisticated statistical help in the future. Statistical analysis programs will be developed that will help the clinician by calculating actual statistical probabilities of progression, taking into account many features of the field, including the probability that several adjacent points may have changed by virtue of random variation as opposed to progressive ocular disease. The present empiric data, and additional data that need to be collected, are important as a basis for these advanced programs. Thus, in the report by Heijl, Lindgren, and Lindgren we get an immediate practical guidance for our present intuitive assessment of the field, but can also imagine the future possibilities for advanced statistical help in making the interpretation.

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LETTERS TO THE JOURNAL

Hypotony Following Instillation of Apraclonidine for Increased Intraocular Pressure After Trabeculoplasty

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Apraclonidine is a topical alpha-adrenergic agonist recently approved by the Food and Drug Administration for prophylaxis against acute intraocular pressure rise after argon laser trabeculoplasty and iridotomy.[1] Hypotony occurred after apraclonidine therapy in a patient who underwent trabeculoplasty.

A 66-year-old man with proliferative diabetic retinopathy developed increased intraocular pressure in his left eye 11 months after a pars plana lensectomy and vitrectomy for vitreous hemorrhage. The anterior chamber angle was open and there was no neovascularization. Although the intraocular pressure was L.E.: 15 mm Hg with timolol maleate 0.5% twice daily, echothiophate 0.125% twice daily, and acetazolamide 500 mg twice daily, the patient reported side effects from the acetazolamide that included intolerable malaise, anorexia, and weight loss. Laser trabeculoplasty was performed in the hope of eventually discontinuing the acetazolamide.

One hour before trabeculoplasty, one drop of apraclonidine hydrochloride 1% was instilled in the left eye. Under topical proparacaine anesthesia, 360 degrees of the anterior trabecular meshwork was treated with 84 evenly spaced applications of blue-green argon laser light, 50-μm spot size, 0.1 second in duration, and 1.1 mW in power. Immediately after the procedure, another drop of apraclonidine hydrochloride was instilled.

One hour after trabeculoplasty intraocular pressure was L.E.: 8 mm Hg. Two hours later intraocular pressure was L.E.: 6 mm Hg. Slit-lamp examination showed an anterior chamber of normal depth with trace cell and flare. There was no evidence of choroidal detachment. The patient was discharged with a regimen of prednisolone acetate 1% four times daily in the left eye. He was instructed to return the next day so that the intraocular pressure increase to normal range could be monitored.

The following day the intraocular pressure was L.E.: 10 mm Hg, and antiglaucoma medications were again withheld. Three days later the anterior chamber was deep and quiet and intraocular pressure was 28 mm Hg. The patient was advised to resume his topical medications and the acetazolamide.

The use of apraclonidine almost certainly contributed to low intraocular pressure observed in this patient. Trabeculoplasty can have an acute intraocular pressure-lowering effect.[2,3] Other causes of decreased intraocular pressure, such as significant inflammation, were not present.

The instillation of apraclonidine hydrochloride 1% in individuals with normal intraocular pressure can result in strikingly low intraocular pressure.[4] In a small percentage of these patients intraocular pressure falls to levels that could potentially be associated with ciliochoroidal detachment and ocular dysfunction. In this patient no adverse effects resulted from the approximately 24-hour period of low intraocular pressure.

THE JOURNAL welcomes letters that describe unusual clinical or pathologic findings, experimental results, and new instruments or techniques. The title and the names of all authors appear in the Table of Contents and are retrievable through the Index Medicus and other standard indexing services. Letters must not duplicate data previously published or submitted for publication. Each letter must be accompanied by a signed disclosure statement and copyright transfer agreement published in each issue of THE JOURNAL.

Letters must be typewritten, double-spaced, on 8 1/2 x 11-inch bond paper with 1 1/2-inch margins on all four sides. (See Instructions to Authors.) An original and **two** copies of the typescript and figures must be sent. The letters should not exceed 500 words of text. A maximum of two black-and-white figures may be used; they should be cropped to a width of 3 inches (one column). Color figures cannot be used. References should be limited to five.

Letters may be referred to outside editorial referees for evaluation or may be reviewed by members of the Editorial Board. All letters are published promptly after acceptance. Authors do not receive galley proofs but if the editorial changes are extensive, the corrected typescript is submitted to them for approval.

These instructions markedly limit the opportunity for an extended discussion or review. Therefore, THE JOURNAL does not publish correspondence concerning previously published letters.

Patients generally are instructed to continue their medications for glaucoma during the first several weeks after trabeculoplasty. In this case, however, I believed it prudent to wait until the intraocular pressure had risen to the normal range before resuming intraocular pressure-lowering medication.

The use of apraclonidine hydrochloride has reduced the risk of increase in intraocular pressure after trabeculoplasty. In addition to monitoring for increased intraocular pressure in these patients, we must also be aware of the possibility of low intraocular pressures when apraclonidine is used. The advent of apraclonidine has not reduced the need to observe patients for two to three hours after trabeculoplasty. Certain patients who develop low intraocular pressure may also need to be examined sooner than one week postoperatively to have intraocular pressure monitored and glaucoma medications adjusted accordingly.

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A New Technique for Optic Disk Analysis in Patients With Glaucoma

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In many patients glaucomatous changes can be detected in optic disk topography and the neuroretinal rim before the visual field changes.[1] It is therefore important to document accurately the optic nerve head of a patient with glaucoma and to have a sensitive method of observation for the detection of changes. Optic nerve head topography can be documented by diagram[2] or by stereoscopic photography.[3] Disk diagrams, however meticulously drawn, cannot capture all the details provided by good stereoscopic disk photographs. Stereoscopic photographs are three-dimensional disk fingerprints that allow better monitoring of patients with glaucoma.

To compare a patient's optic nerve head with previously taken slide disk photographs, the physician must carry a visual imprint of the findings to the remote slide viewer. The detection of subtle glaucomatous progression is dependent on the observer's memory. The greater the elapsed time between disk and slide visualization, the greater the observer error. One should strive for simultaneous comparison between past disk photographs and a current disk examination. I have found a compact stereoscopic viewer (Deep-Vue Corporation, Sun City, Arizona) helps accomplish this. The lightweight viewer measures approximately 5 × 4 × 1¾ inches, is made of plastic, and operates on batteries. The stereoscopic disk slides can be viewed as mounted stereoscopic pairs in masks

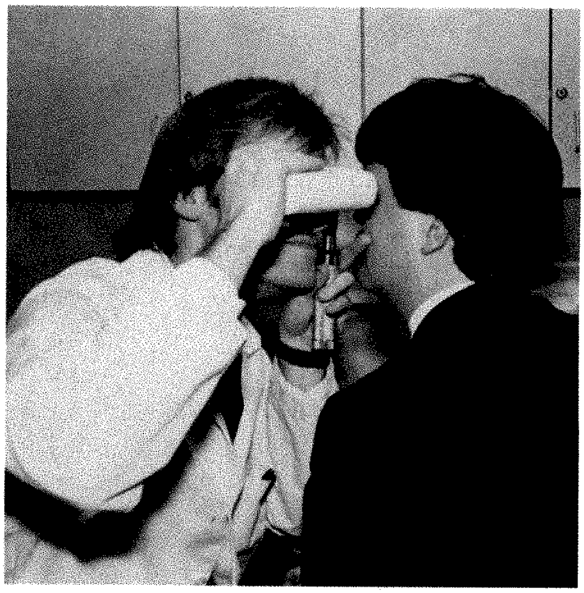

Fig. 1 (Dobrogowski). Simultaneous comparison of the optic disk to a disk photograph using the direct ophthalmoscope and slide viewer.

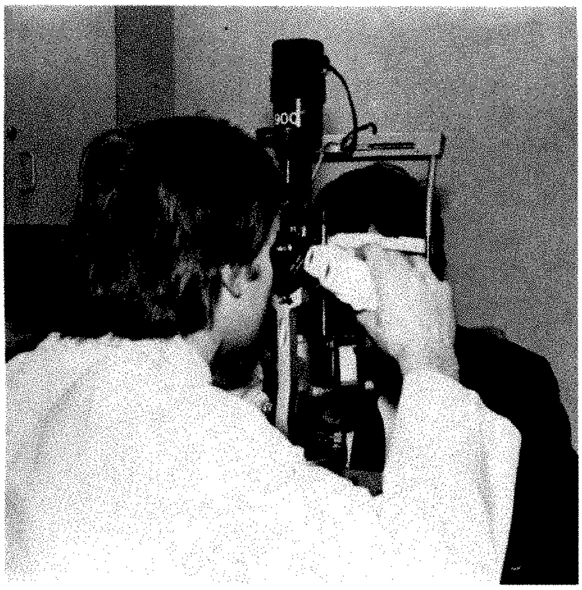

Fig. 2. (Dobrogowski). Comparing the 90-diopter view of an optic disk to stereoscopic disk photographs.

or as two independent slides as part of a stereoscopic pair.

The viewer can be used to compare previous stereoscopic disk photographs with the optic nerve head examined by direct ophthalmoscopy, fundus contact lens, or 90-diopter lens. Simultaneous comparison is possible by looking with one eye through the direct ophthalmoscope at the patient's disk, while looking through one of the viewer's eyepieces with the other eye. By alternately suppressing either eye, direct comparison is achieved. For example, if examining the patient's left optic nerve head, the ophthalmologist observes the patient's disk with the left eye and looks through the viewer with the right eye (Fig. 1). The three-dimensional image of the optic nerve head seen with the fundus contact lens or 90-diopter lens can be rapidly compared to stereoscopic disk photographs by turning away from the slit-lamp oculars and toward the viewer, which is held in the physician's free hand (Fig. 2). For the 90-diopter lens, the slides should be reoriented to match the inverted image formed by this lens.

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Ocular Anomalies in Abdominal Muscle Deficiency Syndrome

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Abdominal muscle deficiency syndrome (also called prune belly syndrome) consists of a triad of congenital deficiencies: absence of abdominal muscles, cryptorchism, and anomalies of the urogenital tract. Talipes equinovarus and pulmonary and gastrointestinal anomalies are also relatively common.[1] The incidence of the abdominal muscle deficiency syndrome has been estimated to be as high as one in 29,000 live births.[2]

Most of the case reports to date describe the urologic features of the syndrome. We studied a patient with abdominal muscle deficiency syndrome who had primary optic atrophy, microcornea, and persistent pupillary membranes.

A 10-month old boy, in whom abdominal muscle deficiency syndrome had been diagnosed, was referred to us for examination. The mother complained that the infant was unable to focus on her face or any object placed before him.

The patient, born of nonconsanguineous parents, had an unremarkable birth and a normal brother and sister. His developmental milestones were delayed. Systemic examination showed dysplasia of the abdominal musculature with distension of the right lateral side, bilateral cryptorchism, and bilateral moderate hydronephrosis. The patient also had talipes equinovarus of both feet (Fig. 1).

On examination, there was no response to light stimulation. Fixation to light was absent and jerk nystagmus was seen on horizontal

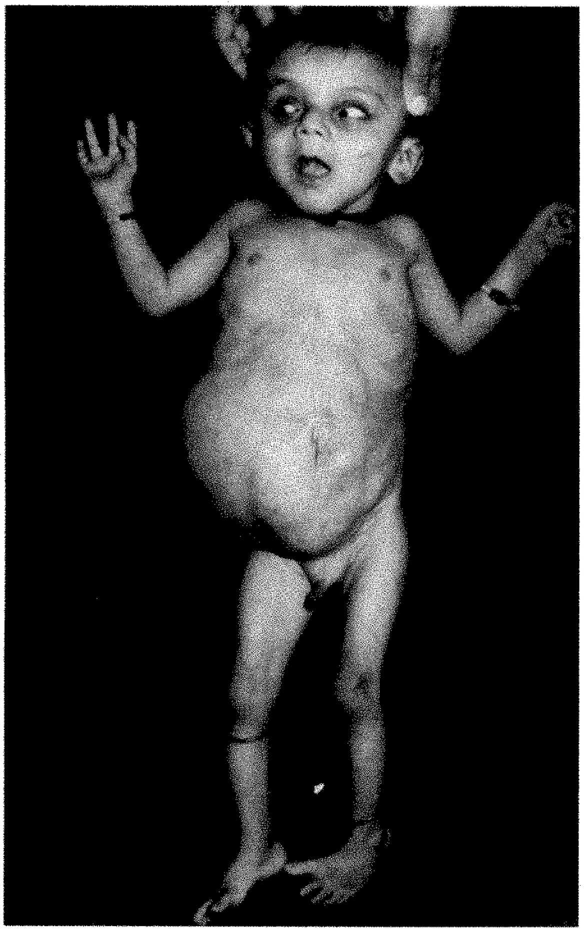

Fig. 1 (Shorey and Lobo). Infant with deficient abdominal muscles, undescended testes, and talipes equinovarus.

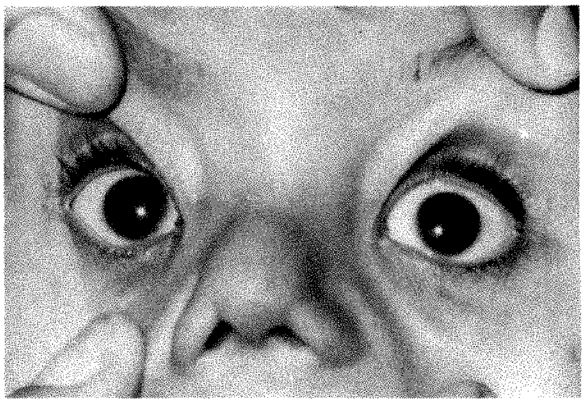

Fig. 2 (Shorey and Lobo). Bilateral microcornea seen in the infant with abdominal muscle deficiency syndrome.

gaze. Anterior segment examination showed bilateral microcornea. The horizontal corneal diameter was 7 mm in each eye (Fig. 2). Persistent pupillary membranes were also seen but were not extensive. The direct and consensual pupillary reactions were sluggish. Primary optic atrophy and hypoplasia of the macula were seen in both eyes on ophthalmoscopy. Intraocular pressure was normal in both eyes. The infant was not cooperative for fundus photography. No optic atrophy, craniofacial anomaly, internal hydrocephalus, or related etiologic factors were noted.

This syndrome may be caused by a general disturbance of embryogenesis between six and ten weeks of gestation, which results in multiple system anomalies.[3] The development of the optic nerve, the visual pathways, and the cornea occurs during this period.[4,5] It is possible that the ocular anomalies seen in our patient are a part of this disturbed embryogenesis. Although an aberration of the mesenchymal development is thought to be central to the findings in this syndrome,[3] the involvement of the neuroectoderm in our patient suggests a wider disturbance of embryogenesis. In autopsy series of this syndrome,[1] the range of anomalies and their incidence is much higher than in surviving patients. This higher incidence may reflect that multiple system anomalies, when present, are inconsistent with life. Hence, ocular anomalies may have gone undetected in such patients.

With improved management of the urologic aspects of this syndrome, more than 50% of these patients have extended life spans.[1] We suggest that patients with abdominal muscle deficiency syndrome routinely undergo an ocular examination to determine if a relationship exists between the ocular anomalies and this syndrome.

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A Nationwide Survey of the Use of Perfluoropropane and Sulfur Hexafluoride

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The unique properties of expansion and persistence have made perfluoropropane (C_3F_8) and sulfur hexafluoride (SF_6) increasingly useful in procedures that require retinal tamponade. In an effort to document and establish their use as the current standard of care, we conducted a nationwide survey to evaluate the extent to which these gases are used by vitreoretinal specialists.

A single-page survey was prepared and mailed to all 1,086 vitreoretinal specialists listed in the 1987–1988 American Academy of Ophthalmology Biographical Membership Directory and Resource Manual. Questions pertained to the location of gas use (office or hospital), type of hospital if used at that location (private, university, county, or veterans/military-related), and practice affiliation of each specialist (private, university, health maintenance organization).

The chi-square statistical method was used to analyze the data for goodness of fit when dealing with a single variable and in contingency table analysis to determine the independence of two variables.

A total of 674 (62.1%) responses were received. Of these, 42 were not used because the respondents were not vitreoretinal specialists even though so listed in the resource manual, were not doing retinal detachment procedures, or had retired. Three surveys were returned because of incorrect address or inability to forward.

Of the 632 usable responses, 458 (72.5%) specialists reported using C_3F_8 or SF_6 in the treatment of vitreoretinal disease. Use of each gas in the office location was nearly equal, with C_3F_8 used by 229 (36.2%) specialists and SF_6 by 230 (36.4%). Use of each gas at the hospital location was greater than that at the office, with C_3F_8 used by 320 (50.6%) specialists ($P < .001$) and SF_6 by 384 (60.8%) ($P < .001$). The SF_6 was used significantly more at a hospital than C_3F_8.

Pooled contingency table analysis showed that C_3F_8 was used consistently more in the university practice setting both at the office ($P < .001$) and hospital ($P < .001$) locations when compared with the private and health maintenance organization practice settings. Similar analyses showed that SF_6 was also used more at the office location in the university practice setting ($P < .005$). When we compared the use of SF_6 between the different practice settings at the hospital location, no significant difference was observed ($P > .10$) (Table).

Preference for gas usage among the different hospital settings was also surveyed. We found that both gases were more frequently used at the private hospital when compared to the university, county, or veterans hospital setting. Moreover, at the private hospital, SF_6 was used to a greater extent than C_3F_8, whereas no difference was observed within the other hospital settings.

In a recent study, Gardener and associates[1] reviewed the extent and current indications for use of air and expansible gases by a select group of retinal surgeons. Our survey encom-

TABLE
USE OF EACH GAS IN EACH PRACTICE TYPE AT OFFICE AND HOSPITAL LOCATIONS*

		C_3F_8		SF_6	
LOCATION	PRACTICE TYPE	NO.	(%)	NO.	(%)
Office	Private	167	(34.8)	169	(35.2)
	University	75	(52.4)	70	(49.0)
	H.M.O.	9	(29.0)	10	(32.3)
Hospital	Private	238	(49.6)	300	(62.5)
	University	99	(69.2)	101	(70.6)
	H.M.O.	17	(54.8)	20	(64.5)

*Based on number of specialists in each practice type as follows: private, 480; university, 143; health maintenance organization (H.M.O.), 31.

passes a much larger population. We also report the amount of gas usage in various locations and practice settings to define more accurately their extent of use. We believe our survey, being the largest to date, documents the widespread use of C_3F_8 and SF_6 across the country, and could provide the basis for establishing their use as the current standard of care.

ACKNOWLEDGMENT

Gary Bradley, Ph.D., Loma Linda University, provided statistical analysis of the data.

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Endogenous Orbital Cellulitis and Endogenous Endophthalmitis in Subacute Bacterial Endocarditis

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Orbital cellulitis usually occurs by direct inoculation after penetrating trauma or by spread of infection from paranasal sinuses.[1] Although rare, infections of the orbit may be secondary to hematogenous spread.[2] We encountered a case of simultaneous endogenous endophthalmitis and endogenous orbital cellulitis caused by metastatic spread from subacute bacterial endocarditis.

A 53-year-old woman was referred because of decreased vision and proptosis of the left eye. She had been admitted three days earlier for low back pain associated with fever and chills. The patient's medical history was significant for rheumatic heart disease, bilateral mastectomies for breast cancer, and chronic depression. The patient had been bedridden because of severe back pain for a week before admission to the hospital.

On examination, visual acuity was R.E.: 20/20 and L.E.: counting fingers. The fundus details were poorly visualized. The left pupil was 5 mm in diameter and poorly reactive to light. The left eye was markedly proptotic with complete ophthalmoplegia. There was associated upper and lower eyelid swelling, conjunctival injection, and chemosis. The patient had a temperature of 104 F, with an increased white blood cell count. Computed tomography of the orbits showed no sinus disease. Blood cultures grew beta-hemolytic streptococci Group G.

A regimen of intravenous penicillin G was started, with complete resolution of the proptosis and ophthalmoplegia within three days. As the orbital cellulitis was resolving, a small (about 10%) hypopyon developed in the left eye. The red reflex was also noted to have decreased, and visual acuity decreased to light perception. Ultrasound showed numerous opacities in the vitreous body. The vitreous changes prevented visualization of the fundus.

Because of the medical history and presence of a holosystolic murmur on physical examination, an echocardiogram was done. The study showed aortic valvular disease, which along with the results of blood culture was consistent with a diagnosis of subacute bacterial endocarditis. The patient's low back pain was caused by septic emboli, resulting in a pyogenic sacroiliitis. The endophthalmitis was presumed to be caused by septic emboli. The patient underwent vitrectomy with administration of intraocular antibiotics. Cultures of the vitreous were positive for streptococcus Group G. Visual acuity, however, never improved.

Meningitis, endocarditis, and urinary tract infections are the most common foci of infection associated with metastatic endophthalmitis.[3] However, concurrent endophthalmitis and orbital cellulitis caused by subacute bacterial endocarditis is unusual. Hematogenous metastasis of an infection to the eye or orbit should always be included as part of a complete differential diagnosis in debilitated patients with decreased vision or proptosis. Early recognition and appropriate management of such cases may improve the visual prognosis in these patients.

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Isolation of HIV-1 From Vitreous Humor

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Human immunodeficiency virus-1 (HIV-1) causes acquired immunodeficiency syndrome (AIDS) by selectively depleting the T4 helper cells in infected individuals. AIDS is also associated with a variety of neurologic and ocular abnormalities. HIV-1 has been isolated from such diverse tissues as peripheral mononuclear cells, bone marrow, lymph nodes, spleen, plasma, semen, saliva, tears, cornea, and retina.[1-3] The most common ocular lesions in AIDS are cotton-wool spots and cytomegalovirus retinitis. These ocular disorders are either the result of direct infection of ocular cells by HIV or may involve interactions with other infectious agents such as cytomegalovirus. In an effort to elucidate the type of ocular tissues that are reservoirs for HIV replication, we carried out virus isolation from ocular tissues of a patient with AIDS.

Eyes were obtained during postmortem examination within two hours of death. The left eye was dissected to separate cornea, retina, sclera, vitreous, and aqueous humor. It had a clear lens and no retinal detachment. The right eye contained a cataractous lens, total retinal detachment, and a pale cupped disk. The vitreous was clear. There was generalized diffuse atrophy and thinning of the retina, which in some areas was thinned to a fine acellular strand. Clusters of degenerating nuclei of the neurosensory retina were observed, but no viral inclusion bodies could be identified. The retinal pigment epithelium showed patchy areas of atrophy and hyperplasia. The optic nerve was atrophic with gliosis and thickening of the pial septa.

Since the HIV antigen has been detected in vitreous humor,[4] we attempted HIV isolation from vitreous humor. Phytohemagglutinin-stimulated peripheral blood lymphocytes from a healthy HIV-seronegative donor were cultured with vitreous humor. Culture supernatants were tested every three days for the production of HIV by reverse transcriptase assay using poly (rA).$(dT)_{12-18}$ as the template primer and Mg^{2+} as the divalent cation. Peripheral blood lymphocytes cultured with vitreous humor showed 82,000 counts per minute of reverse transcriptase activity at the end of three weeks. Both cornea and retinal tissues showed 16,800 and 41,900 counts per minute of reverse transcriptase activity, respectively, upon culturing. The plasma showed viral antigen by enzyme immunoassay and registered 103,400 counts per minute of reverse transcriptase activity upon culturing with peripheral blood lymphocytes.

We also transmitted HIV present in the culture supernatant by inoculating fresh peripheral blood lymphocytes. HIV in the medium was confirmed by nucleic acid hybridization analysis. The pelletted virus from the culture was dissolved in 10 mM Tris, pH 7.5, and 0.5 mM heat-inactivated edetic acid, spotted onto a nitrocellulose filter, and hybridized to a full-length HIV probe.[5] The virus from all the cultures hybridized efficiently to the probe indicating that the virus isolated from the ocular tissues was HIV-1.

Our study indicates that HIV can be isolated from different ocular tissues including vitreous humor. The previous inability to isolate the virus from vitreous humor[3,4] may have resulted from the lack of receptiveness of the cells used for virus replication. HIV-1 has been shown to exhibit extensive heterogeneity.[5] The evolution of the virus in vivo may alter the tropism, cytopathic effects, and replication rate of the

virus. Further study is needed to characterize HIV-1 from different tissue sources.

ACKNOWLEDGMENT

Morey Gardner, M.D., St. Mary's Health Center, St. Louis, referred the patient.

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Isolated Homonymous Hemianopsia in the Acquired Immunodeficiency Syndrome

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Neurologic dysfunction is commonly recognized in patients with the acquired immunodeficiency syndrome (AIDS). Reported incidence is approximately 40% in clinical studies of adult patients.[1] Neuropathologic abnormalities on postmortem examination, however, have been detected in 70% to 80% of patients afflicted with AIDS.[2] About 10% of cases will first manifest as a neurologic disorder.[3] We examined a young, healthy man who developed an isolated homonymous hemianopsia, which was followed by rapid neurologic and systemic deterioration as a result of the human immunodeficiency virus (HIV).

A 34-year-old healthy man developed intermittent and then persistent left-sided visual dysfunction over a six-week period. There was no associated headache, extremity weakness or numbness, diplopia, malaise, Lhermitte's sign, or Uhthoff's symptom. Primary syphilis had been diagnosed ten years earlier and the patient was treated with intramuscular penicillin. Results of physical examination were normal. Neuro-ophthalmic examination showed a total left homonymous hemianopsia with macular splitting on kinetic Goldmann perimetry (Fig. 1). Visual acuity, color vision, pupils, fundi, and optokinetic nystagmus were normal. Magnetic resonance imaging showed multiple areas of abnormal signal primarily affecting the white matter of the right parieto-occipital lobe (Fig. 2), with punctate abnormalities seen in the internal capsule, right thalamus, splenium of the corpus callosum, and frontal lobes. Cerebral vasculitis or demyelinating disease were suspected. Results of lumbar puncture, serum screening for systemic vasculitis, Lyme titer, chest x-ray, and repeat neurologic and physical examinations were unremarkable. The patient was clinically stable for the next two months after which he developed extremity weakness, unsteady gait, difficulty with concentration, and slurred speech. Computed tomography showed well-circumscribed, lucent white matter lesions suggestive of progressive multifocal leukoencephalopathy. Antibodies for HIV were positive. Although the patient was treated with zidovudine and for central nervous system toxoplasmosis and syphilis, there was progressive neurologic deterioration and pneumocystis pneumonia supervened. He died approximately four months after the onset of isolated visual symptoms.

Neurologic disorders in AIDS may be caused by HIV itself or other opportunistic infections, including toxoplasmosis, cryptococcosis, syph-

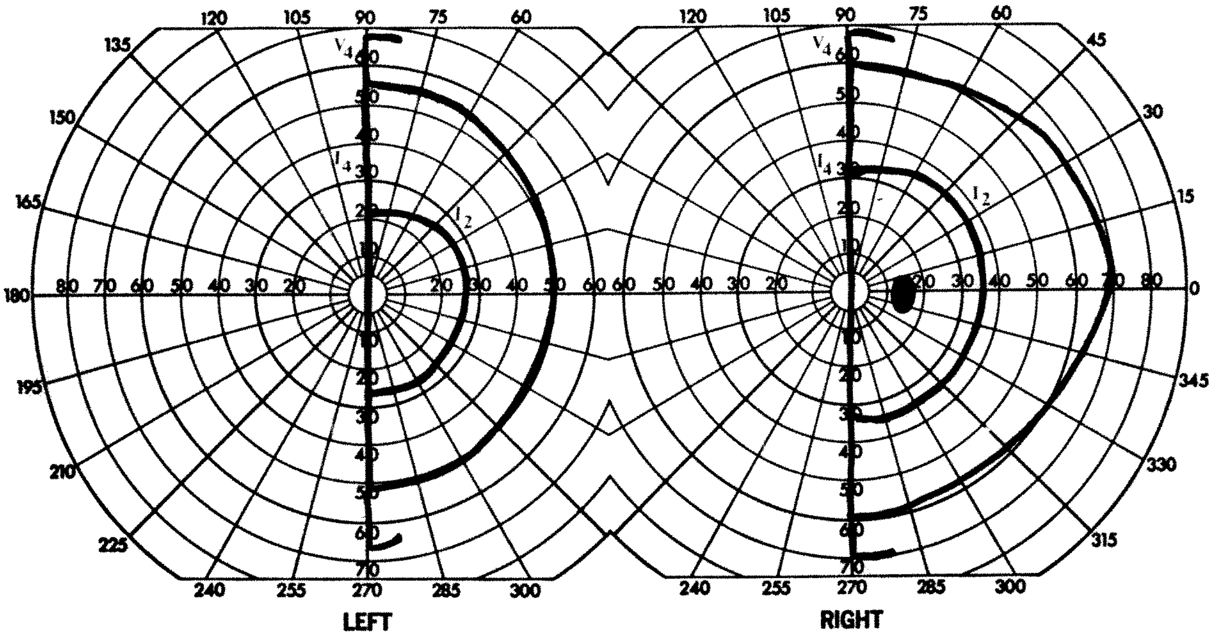

Fig. 1 (Slavin, Mallin, and Jacob). Kinetic Goldmann visual fields showing complete left homonymous hemianopsia with macular splitting.

ilis, cytomegalovirus, progressive multifocal leukoencephalopathy, or neoplasms such as primary central nervous system lymphoma. Progressive multifocal leukoencephalopathy[4,5] is a viral infection (papovavirus JC) of the central nervous system resulting in demyelinating lesions with a characteristic but nonspecific appearance on computed tomography. Be-

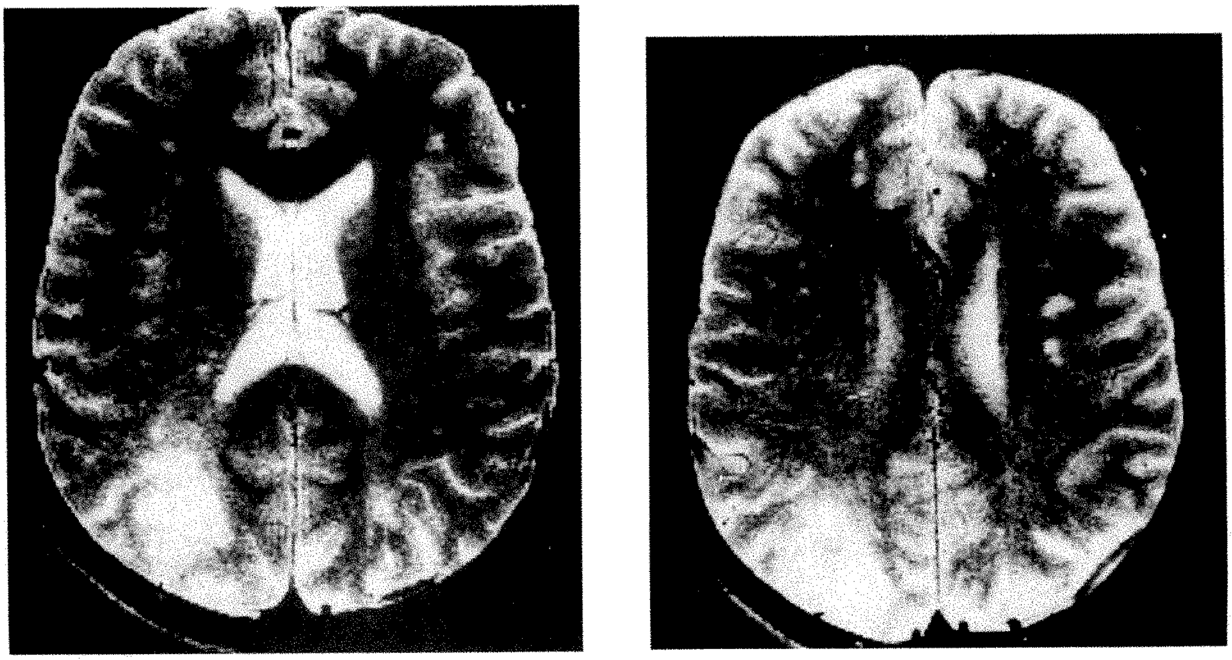

Fig. 2 (Slavin, Mallin, and Jacob). T_2-weighted axial magnetic resonance image through visual cortex (left) shows abnormalities of the white matter of the right parieto-occipital lobes sparing the adjacent cortical mantle. A higher section (right) shows other scattered focal lesions.

fore the early 1980s, it was most commonly seen in patients with immune deficiency caused by chronic lymphocytic leukemia, and Hodgkin's and non-Hodgkin's lymphoma. Common symptoms of progressive multifocal leukoencephalopathy include intellectual impairment, aphasia, memory disturbance, pyramidal tract dysfunction, and homonymous hemianopsia. Neurologic deterioration is often rapid, and death ensues within months. There is no effective therapy. Opportunistic infections in AIDS should be added to the list of differential diagnoses in patients with the sole finding of homonymous hemianopsia.

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An Illuminated Blade for Vitreoretinal Membrane Dissection

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Removal of proliferative membranes from the retinal surface during vitreous surgery is important for successful repair of complicated retinal detachments resulting from proliferative diabetic retinopathy and proliferative vitreoretinopathy. In many cases delamination of the proliferative membranes is required to relieve retinal traction. Frequently a bimanual technique is performed by using scissors in one hand and an illuminated instrument that can engage and elevate the membrane in the other hand. Although illuminated membrane picks allow limited manipulation of membranes, greater control can be achieved by grasping the membrane with forceps and exerting force in various directions to expose the proper surgical plane for sharp dissection. Because adequate illumination of the surgical plane may be difficult without a handheld endoilluminator, we developed an illuminated vitreoretinal blade* that can be used to illuminate and delaminate proliferative tissue simultaneously from the retinal surface while grasping it with intraocular pic-forceps.[1] The illuminated blade (Figure) is 20 gauge in diameter, and consists of a monofilament acrylic optical fiber housed within stainless steel. An extension of the stainless steel housing is fashioned into a blade, the plane of which is angled 45 degrees to the axis of the fiber. The rounded contour of the end of the blade reduces inadvertent penetration of the retina. Both the sides and the end of the blade are sharpened to allow cutting of tissue

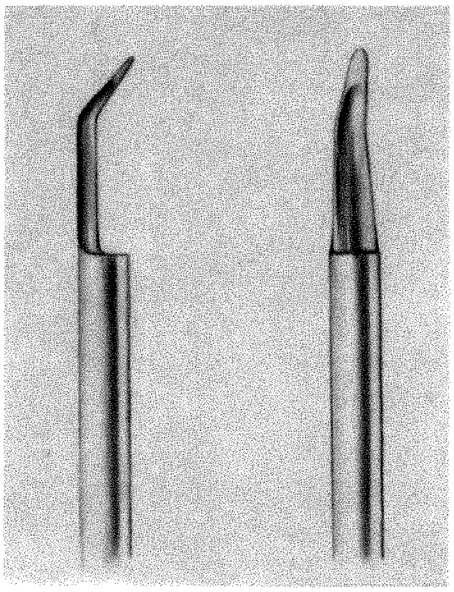

Figure (Han and Abrams). Orthogonal views of illuminated vitreoretinal blade.

*The instrument is available from Trek Products, Mukwonago, Wisconsin.

from various directions. The illuminated blade can be adapted to the currently available light sources for endoillumination.

We found the illuminated blade to be especially useful for en bloc excision of diabetic membranes.[2] The blade can be used as a pick to elevate fibrovascular tissue into the jaws of the pic-forceps, and as a blade to transect its attachments to the retina with a stroking motion tangential to the retinal surface. The technique of simultaneous handheld endoillumination, sharp dissection, and forceps manipulation allows easier identification of the desired surgical plane and reduces the likelihood of iatrogenic retinal breaks compared to the conventional technique of scissors dissection.

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Tonic Pupillary Reaction After Epidemic Nephropathy and Transient Myopia

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Epidemic nephropathy is caused by the Puumala virus[1] and is transmitted mainly by rodents. The disease usually begins with high fever, nausea, backache, headache, oliguria-polyuria accompanied by proteinuria, and hematuria.[2]

The most common ocular symptoms of epidemic nephropathy are transient myopia, edema of the eyelids, and injection and bleeding in the conjunctiva.[3] In some cases acute glaucoma and flare in the anterior chamber are also reported.[4] Pupillary atrophy resulting from iritis may also accompany epidemic nephropathy.[4]

In 1987, 29 cases of epidemic nephropathy were managed in our hospital, which serves 250,000 people. The incidence of diagnosed cases was about 1/10,000. Twenty-six of the patients were male. The patients ranged in age from 15 to 54 years in 28 cases.

We treated a 35-year-old woman whose symptoms were acute high fever, nausea, vomiting, oliguria, and backache. The Puumala virus antibodies in the first blood test were 1:80 and in a second test ten days later 1:320. One year earlier the patient had incurred slight encephalitis after a respiratory infection. During and after that disease she had no ocular symptoms and pupillary reactions were normal.

Four days after the first symptoms distance vision was blurred, first in the left eye and thereafter in the right eye. In the subsequent examination there was −4.0 diopters of myopia in both eyes. There was a slight injection of the bulbar conjunctiva in both eyes and a slight tenderness in the left eye. There was a slight flare in both anterior chambers, more pronounced in the left. The ocular tension was 15 mm Hg in both eyes. The right pupil responded normally to light and convergence, both directly and consensually. The diameter of the left pupil was 8 mm and a tonic pupillary reaction (Adie's pupil) was found. Dexamethasone eyedrops were instilled every second hour during the day and dexamethasone ointment was used at night. Two days later the refraction was −2.5 diopters in the right eye and −2.0 diopters in the left eye. The flare in the anterior chamber had disappeared. Dexamethasone was gradually discontinued. Tendon reflexes were normal and no other abnormal findings were noted on neurologic examination.

In the follow-up examination 45 days after the onset of the disease, the patient still reported photophobia and symptoms of eye strain when reading. Refraction was R.E.: +0.5 +0.5 × 180 and L.E.: +0.75 +1.00 × 180. Visual acuity was 20/20 in both eyes. There was no flare in the anterior chamber and ocular tension was normal. Accommodation was equal. The left pupil was 1 mm larger than the right pupil, and there was a slow reaction to light both directly and consensually but no manifest reaction to convergence was seen. In a dark environment both pupils were sometimes equal and sometimes the left was larger. A drop of 1% homatropine caused symmetric pupillary dilatation to 9 mm in both eyes. One drop of 2% pilocarpine instilled in both eyes thereafter

caused symmetric pupillary constriction to 7 mm within 30 minutes.

Five months later the pupillary status was unchanged. There were no visible differences in pupillary structure or in the pupillary sphincters. One drop of 0.15% pilocarpine was instilled in each eye to demonstrate supersensitivity but no visible reaction in either eye was seen.

The tonic pupillary reflex appears to be connected with acute epidemic nephropathy. It is thought that acute myopia in connection with epidemic nephropathy is caused by edema in the ciliary body with relaxation of the zonulae and protrusion of the lens.[3] In this case epidemic nephropathy caused a lesion in the parasympathetic nerves in the ciliary ganglion or peripheral to it and a tonic pupillary reflex.

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Optic Nerve Head Drusen and Peripapillary Central Serous Chorioretinopathy

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A 24-year-old man came to us because of a shadow slightly temporal to the center in his left eye, which had been present for two days. Ocular history was unremarkable. Uncorrected visual acuity was 20/20 in both eyes. Results of anterior segment examination were normal. Fundus examination showed bilateral large optic nerve head drusen, marked tortuosity of the retinal vessels, and normal maculae. The right fundus was otherwise normal. In the left fundus a peripapillary serous detachment of the sensory retina was observed, with a superonasal extension (Fig. 1). A small yellow subretinal spot was observed in this extension, but no hemorrhages were seen. Two cilioretinal arteries, one located nasally and the other temporally, were noted. Fluorescein angiography showed autofluorescence of the disk drusen, and the superior retinal arteries were seen to originate from the cilioretinal arteries. A bright hyperfluorescent spot was seen superonasal to the disk, corresponding to the yellow spot noted on ophthalmoscopy, surrounded by a few spots of hypofluorescence (Fig. 2). In the late frames there was staining of the subretinal fluid around the leak. An atypical form of central serous chorioretinopathy was diagnosed and the hyperfluorescent spot was interpreted as the retinal pigment epithelium defect responsible for the leakage. A low-intensity laser treatment was applied to the spot (five applications of blue-green argon laser, 150-μm size, 0.2 second, 200 mW). When the patient was seen again ten days later he reported that

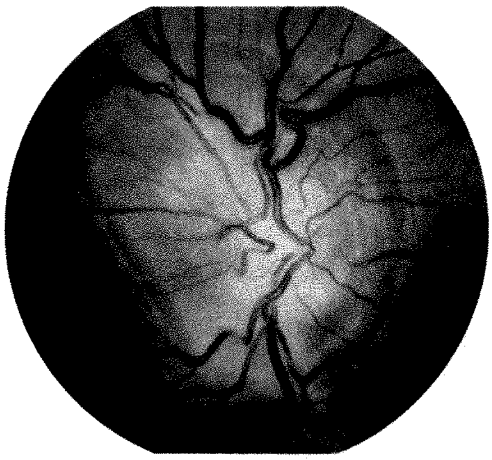

Fig. 1 (Moisseiev, Cahane, and Treister). Peripapillary serous retinal detachment. The drusen are obscured by the fluid.

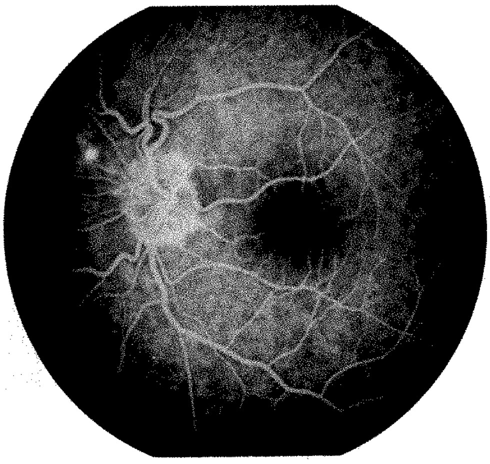

Fig. 2 (Moisseiev, Cahane, and Treister). Fluorescein angiography. A bright hyperfluorescent spot is seen superonasally to the disk.

the scotoma had disappeared five days after treatment. Visual acuity was 20/20 in both eyes. Almost all the subretinal fluid was absorbed. Fluorescein angiography confirmed that the treated area no longer leaked. Follow-up for ten months was uneventful.

Vascular tortuosity and cilioretinal arteries are common in eyes with disk drusen.[1] However, in this case the cilioretinal arteries were responsible for supplying the entire superior half of the retina, and this is rare even in eyes with disk drusen.

Most of the cases where disk drusen are associated with acute visual symptoms result from peripapillary choroidal neovascularization with subretinal hemorrhages.[2] In our patient the exudation was not from a subretinal membrane, but from a retinal pigment epithelium defect similar to that seen in central serous chorioretinopathy. The nasal location of the retinal pigment epithelium defect and the dramatic response to photocoagulation were also unusual.

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L-Shaped Accessory Sponge Exoplant

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Two L-shaped silicone sponge exoplants have recently been developed that may assist in the repair of certain complicated retinal detachments. Sponges 3 and 4 mm in diameter and 40 mm in length have narrow extensions that create an L-shaped contour in cross section (Fig. 1).

These sponges were initially designed to assist in the closure of fishmouth retinal tears. After circumferential scleral buckling with a sponge exoplant, the retinal tear may settle with an elevated anterior flap and posterior radial folds that resist closure. The L-shaped accessory sponge allows the surgeon to broaden the area of scleral indentation in the meridian of the retinal tear. A mattress suture is placed in the appropriate meridian and the accessory sponge is secured behind the encircling element with the extension inserted between the sclera and sponge (Fig. 2). Further modification of the encircling element is unnec-

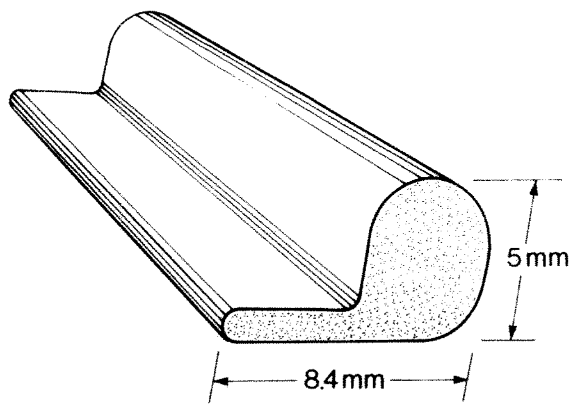

Fig. 1 (Snyder and associates). Cross-sectional dimensions of the exoplant. Each sponge is 40 mm in length.

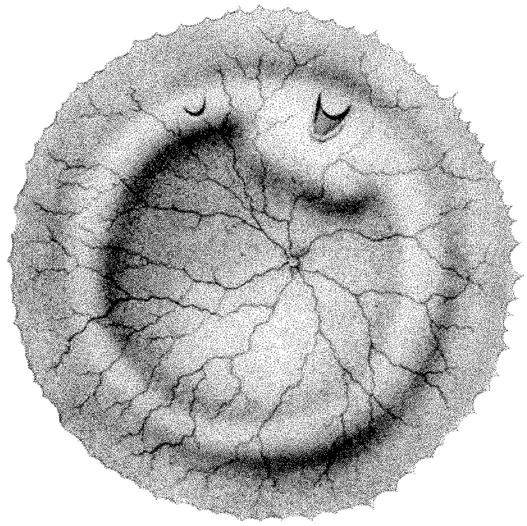

Fig. 2 (Snyder and associates). Accessory sponge secured in the meridian of fishmouth retinal tear.

essary. These accessory sponges have proven to be effective in closing fishmouth retinal tears in our practice over the past three years.

We have also found these sponges to be a valuable adjunct with vitrectomy in our management of proliferative vitreoretinopathy. Broad, high encircling buckles have been advocated in the management of proliferative vitreoretinopathy.[1] Gravitational forces also influence the structure of proliferative vitreoretinopathy with the inferior retina being more involved.[2] In eyes that have had previous scleral buckling in which a broader higher buckling is desirable, we have placed the complete 40-mm length of accessory sponge adjacent to the inferior scleral buckle. If a more posterior supplementation is desired, the accessory sponge is placed posterior to the existing scleral buckle. If there is anterior loop traction, the accessory sponge is secured anterior to the existing scleral buckle. After the existing scleral buckle has been mobilized, two horizontal mattress sutures with broad, secure scleral bites are placed in each quadrant 11 mm apart. The 40-mm length of the accessory sponge generally provides for 180 degrees of indentation. The use of the accessory sponge limits the manipulation of a previously properly placed exoplant and provides a broader, higher scleral buckle in the inferior 180 degrees where proliferative changes are more pronounced. This technique has been used in combination with vitreous surgery for the management of over 100 cases of proliferative vitreoretinopathy.

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Mandibulofacial Dysostosis and Cornea Guttata

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The mandibulofacial dysostosis, or Collins-Franceschetti-Klein syndrome,[1] is characterized by marked malar and mandibular hypoplasia, antimongoloid slant of the palpebral fissures, lower eyelid coloboma, and auricular malformations. Cleft palate and conductive deafness are also present in this condition.

Mandibulofacial dysostosis is reported to have an autosomal dominant transmission with 60% of the cases representing new mutations. In 1975, Johnston[2] proposed that the syndrome is caused by a defect in the neural crest cells migration.

Two girls, 14 and 16 years old, affected by mandibulofacial dysostosis, were referred to us for ophthalmologic examination. Craniofacial dysostosis was diagnosed in the first month of life in both girls. The probands were not relatives, and in both families no one else was affected by the same pathologic condition. The routine examination did not disclose any other abnormalities, except for a mild myopic error in the younger patient. Both patients had corrected visual acuity of 20/20.

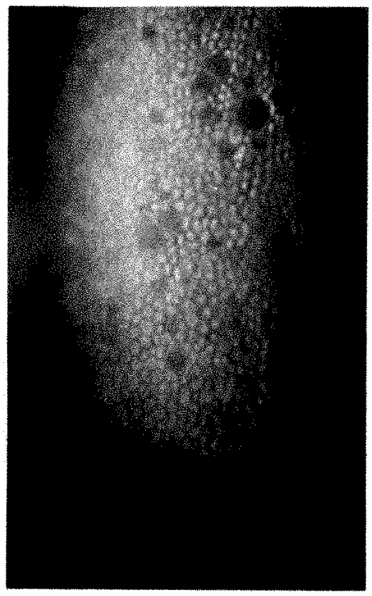

Figure (Nucci and associates). Typical area of cornea guttata in the younger of two affected patients.

To examine other neural crest derivatives we performed a specular microscopy of the corneal endothelial cells. In both cases it showed an irregular mosaic of hexagonal cells in addition to a typical area of cornea guttata (Figure), that we were not able to see on biomicroscopy. The endothelial cell count (2,465 cells/mm^2 in the younger patient and 2,472 cells/mm^2 in the older one) was within normal limits, as was the corneal thickness (472 μm in both subjects). Cornea guttata is now considered to be possibly caused by a neural crest defect,[3] which is, as mentioned above, the same origin of mandibulofacial dysostosis. Additionally, Sulik and associates[4] postulated recently that mandibulofacial dysostosis occurs at the fourth week of gestation. This is the same period in which the first wave of neural crest cell migration takes place, the origin of the corneal endothelium.[5]

Our finding tends to confirm a common embryologic origin of the mandibulofacial dysostosis and cornea guttata, suggesting that ocular neurocristopathies should be looked for in patients with mandibulofacial dysostosis.

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Daily Refractive Changes Persisting After Radial Keratotomy

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I had bilateral radial keratotomy in spring 1985, hoping to obtain right emmetropia and a left postoperative residual myopia of 1.5 diopters. I was 38 years old and had 5 diopters of myopia in each eye. A central clear zone of 3.5 mm was used. In the right eye 12 radial incisions were made; eight were made in the left eye followed by a secondary procedure of four additional radial incisions five months later. I refracted myself immediately after awakening each morning before any other activities by using the examining lane in my home, and then two and 12 hours later in my office under similar lighting conditions.[1]

My right eye responded with a large transient hyperopic shift peaking at two weeks and a generalized hyperopic trend beginning about six months postoperatively (Fig. 1). These two phenomena were superimposed on the daily changes in refraction, which decreased only slightly over the period studied. Three and one half years after radial keratotomy, the right eye refracts as $+4.25 -2.00 \times 95 = 20/30$ one minute after opening the eyes in the morning and as approximately $+3.25 -2.25 \times 95 = 20/20$ during most of the waking hours. Good uncorrected vision despite a large measured residual refrac-

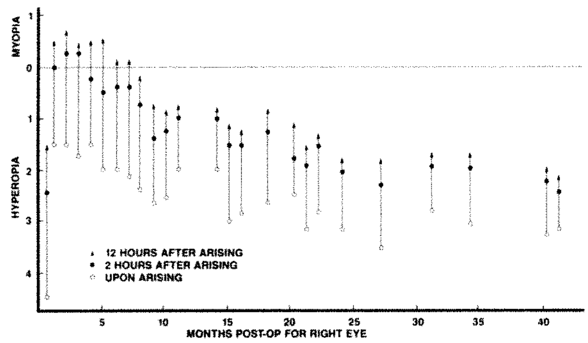

Fig. 1 (Wyzinski). Right eye. Daily refractive changes (as spherical equivalent) after radial keratotomy. Each point is the average of measurements taken on three consecutive days.

tive error after radial keratotomy is not unusual.[2]

My left eye may have had a transient hyperopic shift after the initial radial keratotomy, but no measurements were made at that time (Fig. 2). A transient hyperopic shift did appear after the secondary radial keratotomy, but unlike the right eye, there was no trend to long-term hyperopia and no decrease at all in the amplitude of the daily refractive changes. Three and one half years after radial keratotomy, the left eye refracts as +0.50 −0.50 × 130 one minute after opening the eyes in the morning and as approximately −0.75 −0.75 × 140 during most of the waking hours. I can read Jaeger 1 print with this eye at all times.

In the PERK study, eyes examined during office hours showed an average myopic shift of only 0.27 diopter.[3] About three fourths of my daily myopic shift occurs within the first two hours after arising from bed in the morning. If the full amplitude of this diurnal cycle is to be studied, first morning measurements are essential.

Judging by the modest decrease in amplitude of the daily refractive changes over 3½ years, they may well continue indefinitely. During the first hour after awakening, my left eye contributes to clear distance vision. By the time I am driving to work, the right eye has taken over the task of providing clear distance vision. I have no headache or eyestrain. I read the newspaper at breakfast, perform microsurgery, and drive at night without ever using spectacles or contact lenses.

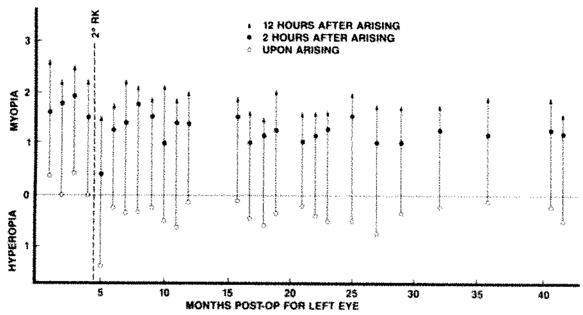

Fig. 2 (Wyzinski). Left eye. Daily refractive changes (as spherical equivalent) after radial keratotomy. Each point is the average of measurements taken on three consecutive days.

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Orbital Hemorrhage in a Newborn

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Unilateral proptosis has been described in association with embryologic malformations in the orbit, such as a dermoid cyst or teratoma; with congenital neoplasms such as retinoblastoma, rhabdomyosarcoma, or neuroblastoma; and with vascular malformations such as hemangioma or lymphangioma.[1] We encountered a case of orbital hemorrhage producing unilateral proptosis in a newborn.

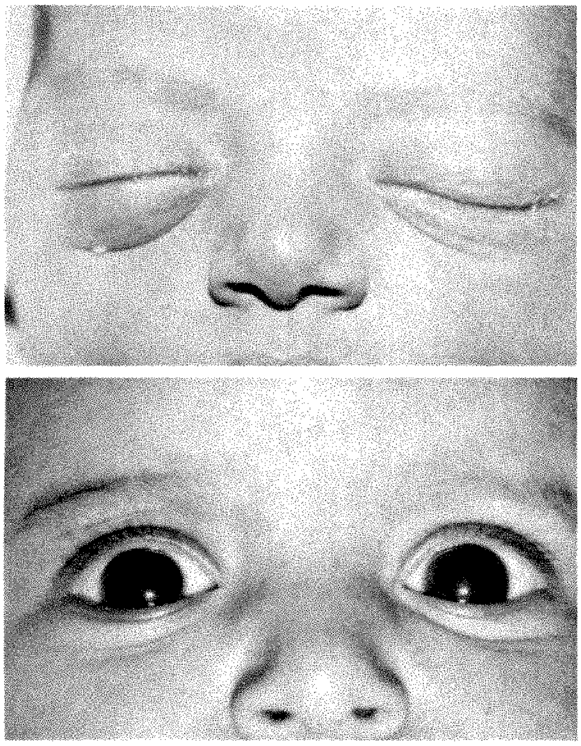

Fig. 1 (Munoz and Weatherhead). Top, The patient preoperatively; bottom, four months after surgery.

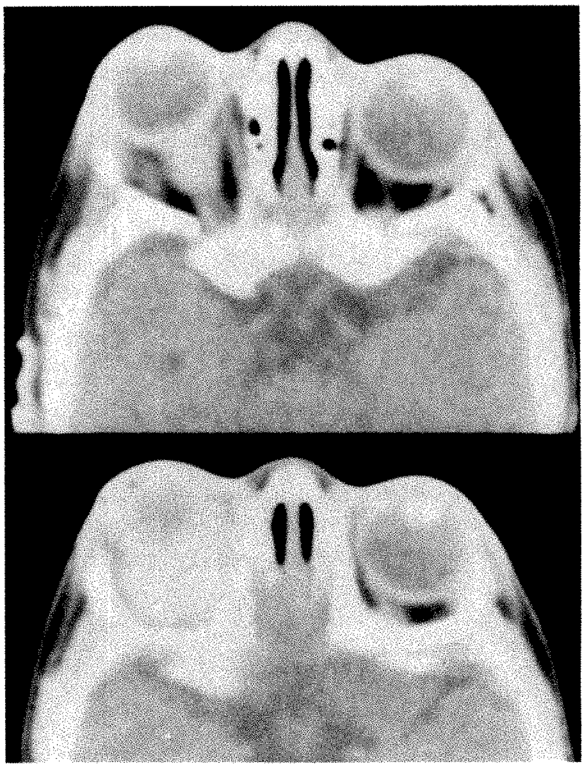

Fig. 2 (Munoz and Weatherhead). Axial computed tomography of orbits shows right extraconal and intraconal mass.

The patient was a 4-day-old boy who had right proptosis since birth (Fig. 1). He was the full-term product of an uncomplicated pregnancy and vaginal delivery in which no forceps had been required. No amniocentesis had been performed during the gestation period. There was no family history of blood dyscrasias or eye tumors.

During our examination we found a right proptosis of 4 mm without pulsations or bruits. There was resistance to retropulsion. Pupils were equal, with no relative afferent pupillary defect, and results of slit-lamp examination were normal. There was mild limitation to elevation in the right eye. The posterior poles were normal and cycloplegic refraction was +1.50 sph in both eyes. The laboratory test results for urinalysis, hematology, and coagulation studies were normal. A pediatric examination disclosed no abnormality.

An echographic examination demonstrated a superior orbital mass with medium to low reflectivity and sound attenuation. No calcium was identified. Computed tomography of the orbits disclosed a large homogeneous mass in the right upper orbit, with extraconal and intraconal extension, and only slight enhancement of the mass when contrast material was used (Fig. 2).

To exclude the possibility of a neoplasm we explored the orbit by using an anterior infrabrow approach. A defect in the periosteum of the superior orbital roof was found. It was associated with an old orbital hematoma with clotted blood products, possibly a subperiosteal hemorrhage that had leaked into the orbit.

The proptosis resolved in the immediate postoperative period. Serial standardized ultrasound examinations have not disclosed any orbital pathologic conditions in the last four months.

The most common cause of orbital hemorrhage is trauma.[2] Even after uneventful deliveries, neonates can have retinal hemorrhages that are probably the result of birth trauma. Possibly birth trauma could produce an orbital hemorrhage.

The possibility of a hemorrhagic diathesis of the newborn can be excluded if the child has a normal bleeding time, or has been given intramuscular vitamin K injections in the nursery.

Usually bleeding from other areas occurs as well.

A small vascular malformation unidentified by ultrasound has not been excluded in our patient, yet the absence of a recurrence to date is encouraging. The six-month follow-up period, however, is short. No invasive investigative procedures have been considered at this time in the absence of new signs. It has been suggested that magnetic resonance imaging might be useful in the diagnosis of blood products in the orbit since they have a typical picture. Chronic hematic cysts occur more commonly in children and can be detected by magnetic resonance imaging.[1,3]

An orbital hematoma should be suspected in a newborn with unilateral proptosis, despite the absence of clotting or vascular disorders, or with a history of uncomplicated delivery. Magnetic resonance imaging might help in the diagnosis and possibly avoid the necessity of surgical intervention, since orbital hematomas often resolve spontaneously.

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An Alternative Needle for Frontalis Suspension

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Frontalis suspension involves suspending the eyelid from the eyebrow with suture or fascia lata passed subcutaneously in a single (for infants) or double rhomboid configuration.[1,2] The main indication for this operation is a large congenital blepharoptosis with minimal levator muscle function.[1,3]

The Wright fascia needle has been used for frontalis suspension for years.[1,3] We used an abdominal needle with a 3/8 circle cutting as an alternative to the fascia needle. The needle (size 2 or 3) is 4 cm in length, ⅓ cm in maximum diameter (Fig. 1). The tissue damage and postoperative reaction are reduced since the abdominal needle is sharper and smaller than the Wright fascia needle. In infants and small children with congenital blepharoptosis the abdominal needle is more efficient since their short and small eyelids make it difficult to use

Fig. 1 (Caputo, Guo, and Wagner). Placement of fascia lata using an abdominal needle.

the Wright fascia needle. It is also useful in patients who have previously undergone blepharoptosis surgery. The eye of the Wright needle is located at the pinpoint, whereas the eye of the abdominal needle is at the opposite end. This allows the abdominal needle to pass through the tissue and make a tissue track for the fascial strip. Less damage occurs in the fascia itself.

Although many different materials have been used to suspend eyelids, fascia lata has proven to be the most successful.[3,4] Fascia lata is preferred to synthetic suture since the latter produces a high incidence of granuloma formation and recurrence of the blepharoptosis.[1,4] We used irradiated fascia lata from the Eye Bank of Wills Eye Hospital with satisfactory results. Two strips of fascia lata were used for each eyelid. They were placed by using the abdominal needle (Fig. 2).[1-3]

Granuloma and abscess around the knots in the eyebrow have been reported to be one of the common complications of fascia use. Reasoning that the ends of the fascia not properly knotted and buried may be responsible for this, one of us (A.R.C.) created split fascia knots in eyebrow incisions. The fascia strips at medial and lateral eyebrow incisions are split after the double rhomboids configuration is completed. The split four ends of the fascia in each incision were double knotted with a piece of suture laid beneath and on top of them (Fig. 2). The knots were deeply buried in the tissue of the eyebrow. We found that the split fascia knots are smaller and easier to tie than those of the nonsplit fascia. In infants and small children a single rhomboid configuration was used.[1]

Ten patients from our institution were included in our study. Seven patients had congenital blepharoptosis with less than 4-mm levator function and two had an associated Marcus Gunn jaw-winking phenomenon. There were no surgical complications in our patients.

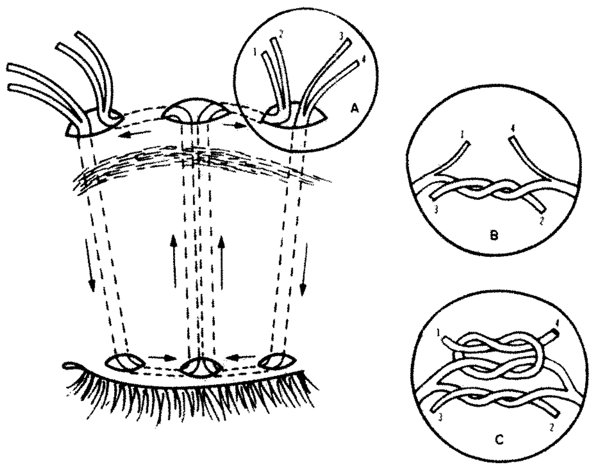

Fig. 2 (Caputo, Guo, and Wagner). The two fascia strips are passed under the skin in the directions of the arrows to complete the two loops. The ends of the split fascia are knotted at the medial and lateral brow incision.

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Correspondence

Correspondence concerning recent articles or other material published in THE JOURNAL should be submitted within six weeks of publication. Correspondence must be typed double-spaced, on 8½ × 11-inch bond paper with 1½-inch margins on all four sides and should be no more than two typewritten pages in length.

Every effort will be made to resolve controversies between the correspondents and the authors of the article before publication.

Trabecular Repopulation by Anterior Trabecular Meshwork Cells After Laser Trabeculoplasty

EDITOR:

In the article "Trabecular repopulation by anterior trabecular meshwork cells after laser

trabeculoplasty," by T. S. Acott, J. R. Samples, J. M. B. Bradley, D. R. Bacon, S. S. Bylsma, and E. M. Van Buskirk (Am. J. Ophthalmol. 107:1, January 1989), the authors should be commended for carrying out a well-designed study that supports the hypothesis that laser trabeculoplasty stimulates trabecular cells to repopulate. By using explants for this study, the investigators were able to simplify the system and to isolate the trabecular meshwork from the vascular system and the mechanical support of the ciliary body. Although this system helped to identify the process of trabecular cellular division by eliminating the role of wandering histiocytes, caution must be taken in the interpretation of this important data regarding the mechanism of action of argon laser trabeculoplasty in glaucoma.

In live monkey eyes we reported extensive biologic activity of the trabecular meshwork in response to laser trabeculoplasty.[1] Several weeks after laser treatment, herniations and vacuolizations of the juxtacanalicular tissue were evident in the nontreated areas and these pouches were infiltrated by chronic inflammatory cells, including plasma cells. Although the role of these cells is unclear, it seems that the integrity of the vascular system and apparently of the ciliary body-trabecular meshwork complex are important for the hypotensive action of laser trabeculoplasty. Although these two important factors are absent in the explant system, it still may be possible to draw conclusions regarding regional differences in cellular division. Therefore, I congratulate the authors for adding another aspect to the complex issue of biologic behavior of the trabecular meshwork in response to laser therapy. A comprehensive understanding of the mechanism of action of laser trabeculoplasty in glaucoma will require more in vivo studies.

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Tel Hashomer, Israel

Reference

1. Melamed, S., Pie, J., and Epstein, D. L.: Delayed response to argon laser trabeculoplasty in monkeys. Arch. Ophthalmol. 104:1078, 1986.

Reply

EDITOR:

We entirely agree with Dr. Melamed's assessment both of the advantages of the organ culture system and with the obvious need to extend the studies to an in vivo, in situ model. We reported results that are consistent with our organ culture studies of in vivo studies in the cat at the recent Association for Research in Vision and Ophthalmology meeting. We have not suggested that trabecular repopulation is the only mechanism of laser trabeculoplasty, but rather a component of the biologic response of the trabecular meshwork to laser.

TED S. ACOTT, Ph.D.
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JOHN M. B. BRADLEY, B.S.
DAVID R. BACON, B.S.
STEPHEN S. BYLSMA, B.S.
E. MICHAEL VAN BUSKIRK, M.D.
Portland, Oregon

Immunohistologic Findings and Results of Treatment With Cyclosporine in Ligneous Conjunctivitis

EDITOR:

In the article "Immunohistologic findings and results of treatment with cyclosporine in ligneous conjunctivitis," by E. J. Holland, C.-C. Chan, T. Kuwabara, A. G. Palestine, J. J. Rowsey, and R. B. Nussenblatt (Am. J. Ophthalmol. 107:160, February 1989), the authors describe the beneficial effects and immunohistochemical findings in two patients with ligneous conjunctivitis following topical application of 2% cyclosporine, 20 mg/ml. Their dosage ranged from hourly to every six hours. Additionally, they reported the absence of any detectable systemic blood levels of cyclosporine and concluded that its effect was primarily local.

We reported[1] the beneficial effects of topical cyclosporine in a series of 11 high-risk corneal allograft recipients at the Association for Research in Vision and Ophthalmology and at

the American Academy of Ophthalmology 1988 meeting. The loading dose was one drop every two hours while awake for four days, beginning 24 to 48 hours preoperatively. Subsequently, all patients were treated with one drop of cyclosporine and one drop of topical prednisolone acetate 1% four times a day for the first three months. The dosage was then gradually reduced, based on the clinical response. Ten of the 11 grafts remained clear at a mean follow-up of 16 months (range, six to 24 months). Using a modified high performance liquid chromatography assay we obtained low but detectable systemic whole blood levels (14 to 64 ng/ml) on three separate occasions.

Cyclosporine is a powerful immunosuppressant with known morphologic and functional nephrotoxic side effects associated with higher systemic levels. Our findings of systemic cyclosporine levels following topical administration suggest that long-term topical therapy must be carefully evaluated before recommending its use for chronic ophthalmic disease. Our preliminary work in high-risk corneal transplants suggests that long-term therapy is necessary to maintain immunosuppression.

Clinical therapeutic blood levels of cyclosporine are routinely measured by either high performance liquid chromatography or radioimmunoassay (polyclonal). The usual detection limit of both the polyclonal radioimmunoassay and high performance liquid chromatography is on the order of 50 ng/ml.[2] Using standard assays, false-negative results can be obtained with low cyclosporine levels. Hamilton and associates[3] reported a highly sensitive high performance liquid chromatography method utilizing acetonitrile protein precipitation and column-switching with sensitivities as low as 2 ng/ml. We used a modified high performance liquid chromatography assay to allow detection of low circulating levels of cyclosporine. The current and previous reported failures to detect systemic blood levels following topical administration of cyclosporine in humans may represent false-negatives caused by lack of assay sensitivity.[4]

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MICHAEL W. BELIN, M.D.
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Reply

EDITOR:

We are well aware of the nephrotoxic side effects of cyclosporine and have reported the clinical and histopathologic effects of long-term cyclosporine use.[1] Early work concerning the pharmacology of cyclosporine, including its use topically, has also been reported by our group.[2,3]

Our study did not recommend the use of topical cyclosporine as a panacea for chronic ocular inflammatory conditions. We described two patients with debilitating ligneous conjunctivitis who responded to this treatment after failing all other treatment modalities. We use a high-performance liquid chromatography assay to monitor blood levels of cyclosporine in patients taking the drug topically. This assay detection limit is 25 ng/ml and is therefore a sensitive measure of systemic levels. More importantly these patients require close monitoring of renal function. Our patients are followed up with serum creatinine and creatine clearance testing. Renal function,

not simply blood levels, is paramount in the detection of cyclosporine toxicity.

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CHI-CHAO CHAN, M.D.
ALAN G. PALESTINE, M.D.
Bethesda, Maryland
J. JAMES ROWSEY, M.D.
Oklahoma City, Oklahoma
ROBERT B. NUSSENBLATT, M.D.
Bethesda, Maryland

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BOOK REVIEWS

Edited by H. Stanley Thompson, M.D.

Perspectives in Glaucoma. Transactions of First Scientific Meeting of The American Glaucoma Society. Edited by M. Bruce Shields, Irvin P. Pollack, and Allan E. Kolker. Thorofare, Slack, Inc., 1988. 297 pages, index, illustrated. $55

Reviewed by Ronald L. Radius
Milwaukee, Wisconsin

As set forth by the editors in their preface, the text is intended to serve a three-part purpose. As the Transactions of the First Scientific Meeting of the American Glaucoma Society, this publication "documents the inauguration of this new society." These transactions also "honor one of the Society's founding members, Charles D. Phelps," whose untimely death occurred only months before the official establishment of the Society. Finally these proceedings fulfill "the desire of the membership ... to share with the ophthalmic community selected current concepts regarding the management of glaucoma."

To these ends, the editors have compiled the contributions of several different authors into a single book. The breadth of the material included in this text and the expertise of the individual contributors are the text's greatest strengths. The single shortcoming of this format is that material originally prepared for an oral presentation does not always transcribe well into text. The time constraints generally imposed upon an oral presentation may limit the amount of information that can be included. The reader may finish some selections wishing that the chapter had been longer. In contrast, other selections may include too much material. Information that may have been valuable as an oral presentation can, as text, make difficult reading indeed.

For the most part, however, the editors have accomplished their task. What were interesting oral presentations have been transformed into readable text. Although some of the topics are of rather selected interest, most of the chapters should be of general interest to the practicing ophthalmologist. Several chapters review current advances in the medical management of glaucoma. There is also a discussion of new surgical techniques used in the operative treatment of glaucoma. Other chapters examine the problems inherent in the evaluation of visual fields, the examination of the retinal nerve fiber layer, and the use of databases and trend analysis in the treatment of patients with glaucoma. The wide range of topics addressed in this book provide reading that will be of interest to both the glaucoma specialist and the general ophthalmologist.

The Book List

Cataract and Refractive Microsurgery. By A. E. Maumenee, W. J. Stark, and I. Esente. Milan, Italy, Fogliazza Editore, 1989. 353 pages, illustrated. $200

Clinical Ophthalmology, ed. 2. By Jack J. Kanski. Stoneham, Butterworths, 1989. 491 pages, index, illustrated. $95

Contact Lenses in Ophthalmology. By Michael S. Wilson and Elisabeth A. W. Millis. Stoneham, Butterworths, 1989. 152 pages, index, illustrated. $49.95

Management of Facial, Head and Neck Pain. By Barry C. Cooper and Frank E. Lucente. Philadelphia, W. B. Saunders, 1989. 368 pages, index, illustrated. $75

Meetings

American Ophthalmological Society—125th Anniversary Meeting

The American Ophthalmological Society, under the aegis of its president, David Shoch, met May 21 to 24, 1989, to celebrate its 125th anniversary at The Homestead, where it had met 48 times in the previous 75 years. The meeting was mellowed by nostalgia as the Society celebrated its anniversary as the oldest national specialty society in the western hemisphere. (The American Psychiatric Association began as the Association of Medical Superintendents of American Institutions for the Insane in 1844, becoming the American Medico-Psychologic Association in 1892, and finally the American Psychiatric Association in 1921.)

Harkening back to the 75th and 100th anniversary celebrations when Traquair and Duke-Elder were honored guests, the Council named Norman Ashton as distinguished honored guest. Other guests of honor included Francisco Contreras of Peru, Alfred Huber of Switzerland, Ridha Mabrouk of Tunisia, Akira Nakajima of Japan, Henri Saraux of France, and Ralph J. Schneider of Canada. Frederick Blodi was the 10th Verhoeff Lecturer, and Frank Newell gave a lecture on the history of the Society.

The Council met on Saturday evening, after their customary spring meeting, but invited the honored guests to their dinner. The chairman of the Council, William Spencer of San Francisco, chaired the arrangements for the meeting. He introduced guests and presented Ashton and Newell with copies of a facsimile of the constitution and the signatures of all members of the Society since its founding and Newell's "The American Ophthalmological Society 1864–1989: A Continuation of Wheeler's History." On Sunday Dr. and Mrs. Morton Cox, the Council, and officers greeted the new associate members elected last year (Augsburger, Philadelphia; Char, San Francisco; Eagle, Philadelphia; Liesegang, Jacksonville, Florida; Small, Oklahoma City; and Van Buskirk, Portland, Oregon). Each gave a paper at the scientific sessions. The meeting opened officially with the reception for new members on Sunday evening.

The scientific program opened Monday morning with a special lecture on the history of the Society by Frank Newell. The regular scientific program followed. The special guests were entertained at lunch by the Council and officers. Professors Henri Saraux of France, Mabrouk of Tunis, Tunisia, Francisco Contreras of Peru, and Alfred Hubel of Switzerland spoke briefly.

That evening at the executive session Leonard Christiansen kept the members in suspense as he recounted the childhood and career of the Howe medalist, Marshall Parks. Robert Kennedy, of Rochester, New York, was named president to succeed David Shoch. Frederick Blodi, of Iowa City, was named vice president to succeed Kennedy. Thomas P. Kearns of Rochester, Minnesota, who served as editor of the Transactions (1973–1979) and secretary-treasurer since 1981 was succeeded by W. Banks Anderson of Durham. Robert B. Welch of Baltimore continues as editor of the Transactions. William Tasman of Philadelphia succeeds Banks Anderson as assistant editor. Richard Richards of Baltimore who served as program chairman (1982–1985) was named to the Council.

This is the only remaining national ophthalmic meeting that still has a program covering all phases of ophthalmology and that permits an unlimited number of discussants. Changes though are evident; papers that would have stimulated wide discussions in the past had but a single discussant. The host of super specialists in the audience discouraged the once common description of the history and management of an interesting patient. Unlike former years the opening discussions were often more critical and demanded better statistical controls and more adequate long-term observation of patients.

The 10th Verhoeff lecture by Frederick Blodi was a scholarly exposition of the events in medicine in 1864 and ranged from a description of medical journals and books to scientific meetings. It was exceptionally well done. The paper by Daniel Albert and his coworkers on transgenic mice that have a gene for a trilateral retinoblastoma was outstanding. The defect has been bred through several generations with 75% of the offspring that have the gene developing bilateral retinal tumors and midline nervous system tumors.

The annual banquet, with William Spencer presiding, was the highlight of the meeting. He introduced the guests of honor and President Shoch introduced Norman Ashton, distinguished guest of honor who proposed the toast to the Society. Shoch responded and Robert Kennedy, president-elect, gave the toast to the guests. Akira Nakajima of Japan responded. The evening closed with announcement of the winners of the various contests that ranged from golf and tennis to fishing and bowling.

The meeting was a fitting celebration of the 125th anniversary of the Society. The next meeting will be May 20 to 23, 1990, at The Homestead. W. Richard Green is the program chairman.

FRANK W. NEWELL

Historic Vignettes

The Lancaster Course

At the end of World War II the need for orientation and refresher training for homecoming physicians was recognized in the field of ophthalmology by Walter B. Lancaster, Theodore L. Terry, and S. Judd Beach among others. These men organized the Ophthalmological Study Council to give the course, which is now named the Lancaster Course in Ophthalmology. It was first given in Boston in March 1946, and again in the autumn of that year in St. Petersburg, Florida. Some of the attending students had been general practitioners, others were applicants for various residency programs. The sudden death of Dr. Terry during the first session marked the loss of a great investigator and teacher.

The faculty has always been recruited from many institutions across the United States, with a few from Canada. Charter members of the Faculty included Albert E. Sloane and Albert N. Lemoine. Paul Boeder taught Optics almost from the beginning until his retirement in 1986. More than 100 ophthalmologists have taught in the Course over the years, most of them still living. The present Faculty comprises about 20 members from the Boston area and 30 from other parts of the country.

The first course was given at the Boston Medical Library. In 1948 the Course moved to Westbrook Junior College in Portland, Maine. Since 1953 it has been given at Colby College, Waterville, Maine, as one of that institution's Special Programs, which vary from estate planning, church organists, to an orthopedic surgery review course. The Kevin Hill Course in Ophthalmology, an offshoot of the Lancaster Course, is given for four half-days in August.

Upon Dr. Lancaster's retirement in 1948, Parker Heath became director of the Ophthalmological Study Council. He moved the course to Colby in 1953. In 1962 he appointed Mrs. Jeanne Hammond to be secretary of the Course, and she continues as Executive Secretary to this day. I succeeded Dr. Heath as Director in 1966. The following year I secured the sponsorship of the Massachusetts Eye and Ear Infirmary for the Course.

Among past and present greats of the Course one must include Peter Kronfeld, Phillips Thygeson, Trygve Gundersen, Arthur Linksz, Russell L. Carpenter, Marshall Parks, and David Guyton. Dr. Carpenter's incomparable collection of slides of the normal eye and adnexa is still in use for individual microscopic study by all of the students in the first week. One of the most popular sections of the course is Ophthalmic Pathology under the able direction of William C. Frayer since 1966.

During the 46 years that the Course has been given there have been about 5,000 students. Enrollment has dipped below 100 for the first time in 25 years, and the future of the course will depend upon the trend toward in-house instruction by the various residency programs, about 100 in all, which have sent students to the Lancaster Course over the years.

All alumni and alumnae of the Course are urged to update their current addresses by writing to Mrs. Jeanne L. Hammond, Lancaster Course, Colby College, Waterville, Maine 04901.

Reprint requests to Henry Freeman Allen, M.D., Black River Farm, 1159 Pottersville Rd., Chester, NJ 07930.

HENRY FREEMAN ALLEN

ABSTRACT DEPARTMENT

Edited by David Shoch, M.D.

American Journal of Pathology

Immunohistochemic localization of blood-retinal barrier breakdown in human diabetes. Vinores, S. A., Gadegbeku, C., Campochiaro, P. A., and Green, W. R. (Dept. Ophthalmol., Univ. Virginia School of Med., Charlottesville, VA). Am. J. Pathol. 134:231, 1989.

A breakdown of the blood-retinal barrier is frequently seen in diabetic retinopathy. To determine the site of this breakdown the authors examined paraffin-embedded eyes from patients with various stages of diabetic retinopathy and compared their findings to those in normal patients with no history of diabetes. This was done by immunohistochemical staining of albumin. As might be expected, no extravascular albumin was detected in the retinal pigment epithelium of nondiabetic patients. However, there was a direct correlation between the severity of the diabetic retinopathy and the degree of extravascular albumin. When proliferative diabetic retinopathy was present, 90% of the cases showed extravasation. The inner retinal vasculature appeared to be the primary site of leakage. An eye from a patient with cytomegalic virus retinitis showed albumin staining predominantly in the inner retina, whereas an eye that had a retinal detachment showed outer retina staining. (3 figures, 1 table, 24 references)—David Shoch

Archives of Otolaryngology, Head and Neck Surgery

Superior and transantral orbital decompression procedures. Stanley, R. J., McCaffrey, T. V., Offord, K. P., and DeSanto, L. W. (Dept. Otorhinolaryngol., Mayo Clin., 200 First St. S.W., Rochester, MN 55905). Arch. Otolaryngol. Head Neck Surg. 115:369, 1989.

The authors increased the intraorbital pressure in 16 cadaver orbits by inserting a catheter and balloon through the orbital foramen. All the pressures were increased to the same level by instilling 9 to 12 ml of air into the balloons. The orbits were then decompressed either from above or transantrally. In both cases the maximum decompression occurred when one complete wall was removed. Incising the periorbita did not decompress the orbits much more but reduced the exophthalmos as the orbital fat herniated through the opening in the periorbita. Since the amount of decompression is the same with both approaches, the authors advise a transantral approach as the first procedure since this is associated with less morbidity than the superior approach. However, if the lesion in the orbit lies at the apex then a superior approach may be preferable since it allows direct access to the area. (8 figures, 9 references)—David Shoch

Clinical and Experimental Immunology

Immunohistochemical analysis of the retrobulbar tissues in Graves' ophthalmopathy. Weetman, A. P., Cohen, S., Gatter, K. C., Fells, P., and Shine, B. (Dept. Med., Level 5, Addenbrookes Hosp., Cambridge, CB2 2QQ England). Clin. Exp. Immunol. 75:222, 1989.

The authors studied biopsy specimens of muscles from three patients with Graves' ophthalmopathy. The specimens had been obtained up to 29 years previously. They also performed studies on frozen sections from retrobulbar fat and connective tissue obtained more recently. They confirmed that most of the infiltration is in the extraocular muscles and is composed primarily of T lymphocytes. B cells were also found but were primarily in focal aggregates. The orbital fat and connective tissue contained few lymphocytes. The results indicate that Graves' ophthalmopathy is primarily a T-cell disease and to a lesser extent a B-cell response against retrobulbar tissues. The authors postulate that the extraocular muscle interstitial cells may be the targets of activation. (6 figures, 24 references)—David Shoch

Journal of Cataract and Refractive Surgery

Advantages and limitations of current soft intraocular lenses. Neumann, A. C., and Cobb, B.

(Neumann Eye Inst., 801 N. Stone St., DeLand, FL 32720). J. Cataract Refract. Surg. 15:257, 1989.

The authors evaluated six soft intraocular lenses, five of them made of silicone and one of hydrogel. There are several disadvantages to these lenses, including that they come in only one size, which can lead to decentration and even subluxation in large eyes. The techniques of insertion also pose some risk of intraocular damage and wound stretching if the lenses are inserted via a 3- to 3.5-mm incision. Additionally, folding grooves remained in some of the lenses and pigment dispersion was associated with the hydrogel lens. The authors presently recommend the use of small diameter polymethylmethacrylate implants for small incision cataract surgery. (7 figures, 4 tables, 13 references)—David Shoch

Journal of Clinical Investigation

Correlation of fibrosis and transforming growth factor-β type 2 levels in the eye. Connor, T. B., Roberts, A. B., Sporn, M. B., Danielpour, D., Dart, L. L., Michels, R. G., de Bustros, S., Enger, C., Kato, H., Lansing, M., Hayashi, H., and Glaser, B. M. (Wilmer Ophthalmol. Inst., Maumenee 119, Johns Hopkins Hosp., 600 N. Wolfe St., Baltimore, MD 21205). J. Clin. Invest. 83:1661, 1989.

Qualitative studies have shown that transforming growth factor-β can enhance fibrosis leading to traction retinal detachment. The authors attempted to define the levels of transforming growth factor-β in relationship to fibrosis by aspirating vitreous from eyes with intraocular fibrosis associated with proliferative vitreoretinopathy. They found that these eyes have three times the amount of transforming growth factor-β than is present in eyes with uncomplicated retinal detachments without intraocular fibrosis. They also blocked this activity with specific antibodies against transforming growth factor-β_2, whereas only 10% to 20% could be blocked by specific antibodies against transforming growth factor-β_1. Transforming growth factor-β_1 when combined with fibronectin can be used to produce intraocular fibrosis in the vitreous cavity of rabbits. This provides a model for further study of this entity. (4 figures, 2 tables, 33 references)—David Shoch

Journal of the National Cancer Institute

Frequency of 13q abnormalities among 203 patients with retinoblastoma. Bunin, G. R., Emanuel, B. S., Meadows, A. T., Buckley, J. D., Woods, W. G., and Hammond, G. D. (Childrens Cancer Study Group, Operations Office, 3rd Fl., 199 N. Lake Ave., Pasadena, CA 91101). J. Natl. Cancer Inst. 81:370, 1989.

The peripheral blood lymphocytes of 203 patients with retinoblastoma were studied for variation in karyotypes. Of the 203 patients, 12 had chromosomal abnormalities involving the long arm of chromosome 13. Of these 12, six had unilateral retinoblastoma and six had bilateral disease. Ten patients had deletions, two of them mosaic and eight nonmosaic. None of the ten patients with familial retinoblastoma had a visible cytogenetic abnormality. Of note were the patients with unilateral retinoblastoma who had abnormalities of chromosome 13, which would have been classified as sporadic had it not been for cytogenetic analysis. The incidence of mosaic deletions is lower in this series than that previously reported. (3 tables, 18 references)—David Shoch

Mechanisms of Ageing and Development

Fibronectin detection in drainage outflow system of human eyes in ageing and progression of open-angle glaucoma. Babizhayev, M. A., and Brodskaya, M. W. (Moscow Helmholtz Res. Inst. of Eye Dis., Sadovaya-Chernogryaxskaya, 14/19, Moscow, 103064 U.S.S.R.). Mech. Ageing Dev. 47:145, 1989.

Recently, the extracellular glycoprotein, fibronectin, has been identified in the trabecular meshwork and in the inner wall of Schlemm's canal. The authors hypothesized that there is an increase in fibronectin deposit with aging and in open-angle glaucoma that accounts for the change in the resistance to aqueous humor outflow. To test this hypothesis the authors obtained material from four donor eyes that had normal intraocular pressure in life and trabeculectomy specimens from 23 patients with uncontrolled open-angle glaucoma. The fibronectin in the specimens was identified by indirect immunoperoxidase labeling. Morphometric evaluation of immunoperoxidase staining showed a definite quantitative increase

in fibronectin content of the inner wall of Schlemm's canal with aging and also with moderately advanced and advanced glaucoma. Fibronectin levels in tissues from healthy adults over 70 years of age were not significantly different from those found in advanced glaucoma. (4 figures, 2 tables, 24 references)—David Shoch

Neurology

Downbeating nystagmus and other ocular motor defects caused by lithium toxicity. Corbett, J. J., Jacobson, D. M., Thompson, H. S., Hart, M. N., and Albert, D. W. (Dept. Neurol., Univ. Iowa College of Med., Iowa City, IA 52242). Neurology 39:481, 1989.

A 63-year-old woman died after an accidental lithium overdose. Her ocular findings included a horizontal gaze palsy and downbeat nystagmus. Postmortem study showed that there was an almost total loss of cells in the nuclei propositus hypoglossi. Thus, it would seem that these nuclei are the neural integrators for premotor processing in the ocular motor system. Similar types of ocular motor lesions have resulted from experimentally produced lesions in the nuclei propositus hypoglossi in monkeys. However, other types of ocular defects have been reported with lithium toxicity, including gaze-evoked nystagmus, unilateral gaze palsy, oculogyrate crisis, and opsoclonus. The wide variety of responses makes it evident that structures other than the nuclei propositus hypoglossi can also be affected by lithium. (2 figures, 2 tables, 40 references)—David Shoch

Plastic and Reconstructive Surgery

The oculocardiac reflex in blepharoplasty surgery. Matarasso, A. (1009 Park Ave., New York, NY 10028). Plast. Reconstr. Surg. 83:243, 1989.

The authors found that one fourth of the patients undergoing blepharoplasty exhibited the oculocardiac reflex as defined by a greater than 10% decrease in the preoperative heart rate. The patient most likely to demonstrate this reflex was a young, anxious female, with a history of cardiac disease. Other important factors were light anesthesia and aggressive fat pad resection. The reflex occurred most commonly during traction on the medial fat pad. Release of traction permitted the heart rate to return to normal. The authors advise continuous visible as well as audible monitoring of the cardiac rate and stress the importance of an emergency crash cart for cardiac resuscitation when performing blepharoplasty. (7 figures, 1 table, 45 references)—David Shoch

Blepharospasm and its treatment, with emphasis on the use of botulinum toxin. Borodic, G. E., and Cozzolino, D. (100 Charles River Plaza, Boston, MA 02114). Plast. Reconstr. Surg. 83:546, 1989.

The authors reviewed the technique of botulinum injection for the treatment of blepharospasm. They followed up 94 patients for an average of 11 months, with only a 10% dropout rate. Average beneficial effect for the patients with benign essential blepharospasm was 3½ months. For hemifacial spasm the effect of treatment lasted about five months. With repeated injections the doses required to achieve the therapeutic effect appeared to increase, but eventually leveled off. Although this technique does not provide a permanent cure, it does give relief and in some cases is useful as an adjunct to traditional surgery. (9 figures, 4 tables, 36 references)—David Shoch

Complications of oriental blepharoplasty. Weng, C. J., and Noordhoff, S. (Chang Gung Mem. Hosp., Dept. Plast. Surg., 199, Tung Hwa North Road, Taipei, Taiwan 105, Republic of China). Plast. Reconstr. Surg. 83:622, 1989.

The eyelids of oriental persons are generally characterized by an absent skin fold, which results in fullness of the supratarsal area. This is sometimes associated with epicanthal folds as well. In most cases the deformity is cosmetic, but fullness of the eyelid may allow some entropion to occur with irritation of the globe by the eyelashes. The most common mechanism of repair is creation of a supratarsal fold by simple stitch fixation. The authors studied 42 patients who developed complications after blepharoplasty to create an eyelid fold. The most common complication found in one third of the patients was asymmetry, with one eyelid fold being higher than the other. The next most common complications were retraction and

blepharoptosis. In both of these complications the fixation of the eyelid is well above the upper edge of the tarsus. The retraction appears to be caused by adherence of the orbital septum to the levator aponeurosis. This complication is probably the result of excessive manipulation of the levator tissue and the orbital septum. Finally, some patients experienced a gradual loss of the eyelid fold because of either a lack of inclusion of the dermis or the use of absorbable suture material. (10 figures, 1 table, 15 references)—David Shoch

Conchal cartilage and composite grafts for correction of lower lid retraction. Marks, M. W., Argenta, L. C., Friedman, R. J., and Hall, J. D. (Sec. Plast. & Reconstr. Surg., Bowman Gray School of Med., Wake Forest Univ. Med. Ctr., 300 S. Hawthorne Rd., Winston-Salem, NC 27103). Plast. Reconstr. Surg. 83:629, 1989.

The authors describe a technique of using ear cartilage to replace missing structural tissues of the lower eyelid in repair of the medial or lateral canthus. If there is a shortage of skin then a composite graft is taken from the ear by using skin as well. The natural curvature of the conchal cartilage makes it an ideal material. Since it is taken from the patient there is no danger of rejection. The authors warn that the cartilage must be carefully thinned and trimmed to fit the defect particularly on the lateral side where the overlying skin is thin. (6 figures, 2 tables, 8 references)—David Shoch

Stroke

Atherosclerosis potentiates constrictor responses of cerebral and ocular blood vessels to thromboxane in monkeys. Faraci, F. M., Williams, J. K., Breese, K. R., Armstrong, M. L., and Heistad, D. D. (Dept. Intern. Med., Cardiovascular Ctr., Univ. Iowa College of Med., Iowa City, IA 52242). Stroke 20:242, 1989.

Thromboxane can be produced by blood vessel walls or be released from platelets during aggregation. It has been shown that atherosclerotic blood vessels produce twice as much thromboxane as normal vessels. Atherosclerotic vessels also show increased vasoconstriction in response to serotonin released from platelets. To evaluate the effect of these agents on blood flow to the eye in normal and atherosclerotic monkeys the authors infused both serotonin and a thromboxane analogue termed U46619 into one carotid artery. They found that serotonin had no effect on blood flow to the eye in normal monkeys but decreased flow to the retina and choroid in atherosclerotic monkeys by almost 50%. Similarly, the thromboxane analogue had no effect on blood flow to the eye in normal monkeys but decreased blood flow to the eye by about 60% in atherosclerotic monkeys. Thus, atherosclerosis potentiates effects of thromboxane and serotonin on blood flow to the eye. (3 figures, 2 tables, 26 references)—David Shoch

Occipital infarction with hemianopsia from carotid occlusive disease. Pessin, M. S., Kwan, E. S., Scott, R. M., and Hedges, T. R. (Dept. Neurol., Tufts-New England Med. Ctr., 750 Washington St., Boston, MA 02111). Stroke 20:409, 1989.

Occipital infarction with hemianopsia usually results from occlusion of the posterior cerebral artery, which originates in the basilar-vertebral system. In the patient described, the basilar-vertebral system was intact with a plaque occlusion in the internal carotid system as demonstrated by embolus in the right fundus and a carotid bifurcation bruit. An angiogram showed communication between the right internal carotid artery and the vertebrobasilar circulation via a fetal right posterior communicating artery. The right posterior communicating artery was intact and patent, with no evidence of occlusions. Thus, a congenital anomaly should be suspected in cases of posterior vascular disease in the presence of an intact vertebrobasilar/posterior communicating artery system. (3 figures, 9 references)—David Shoch

NEWS ITEMS

Send News Items to
American Journal of Ophthalmology
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The Journal invites readers to submit announcements concerning meetings, postgraduate courses, lectures, honors, and appointments. Each item must be typed double-spaced on bond paper with 1½-inch margins. Only one news item should be submitted on each page. Announcements concerning meetings and courses must contain the title, location, dates, sponsors, and address required for additional information. Each item must not exceed 75 words in length and be prepared in narrative, not outline, form. Announcements of meetings and courses must be received at least four months before the event.

Biomaterials in Ophthalmology: First Interdisciplinary Symposium

Biomaterials in Ophthalmology: First Interdisciplinary Symposium will be held Sept. 1–4, 1989, in conjunction with the Ninth Centennial of the University of Bologna. For further information, write Dr. Piera Versura, Scientific Secretariat, Institute of Ophthalmology, Via Massarenti, 9, 40138 Bologna, Italy.

American Electroencephalographic Society: Annual Course in Clinical EEG and Electrophysiology and Annual Meeting

The American Electroencephalographic Society Annual Course in Clinical EEG and Electrophysiology and Annual Meeting will be held Sept. 21–24, 1989, at the Sheraton New Orleans Hotel, in New Orleans. For further information, write, Jacquelyn T. Coleman, Executive Director, AEEGS, P.O. Box 30, Bloomfield, CT 06002; telephone (203) 243-3977.

Division of Ophthalmology—Saint Luke's Hospital, Cleveland: Fourth Annual Tilles-Weidenthal Lecture

The Division of Ophthalmology—Saint Luke's Hospital, Cleveland: Fourth Annual Tilles-Weidenthal Lecture will be given by Jerry A. Shields, Sept. 23, 1989. For further information, write Daniel T. Weidenthal, M.D., Director, Division of Ophthalmology, Saint Luke's Hospital, 11311 Shaker Blvd. Cleveland, OH 44104; telephone (216) 368-7146.

Retina Center at Saint Joseph Hospital, Baltimore: Management of Complicated Retinal Detachments Course

The Retina Center at Saint Joseph Hospital, Baltimore: Management of Complicated Retinal Detachments Course will be held Oct. 6 and 7, 1989. For further information, write The Retina Center at Saint Joseph Hospital, P.0. Box 20,000, Baltimore, MD 21284; telephone (301) 337-4500.

University of Maryland: Ninth Annual Clinical Conference Current Concepts in Ophthalmology and Third Annual Lois A. Young-Thomas Memorial Lecture

The University of Maryland: Ninth Annual Clinical Conference Current Concepts in Ophthalmology and Third Annual Lois A. Young-Thomas Memorial Lecture will be held Sept. 15, 1989, at the Hyatt Regency Hotel On the Inner Harbor, Baltimore. For further information, write Program of Continuing Education, 655 W. Baltimore St., Baltimore, MD 21201; telephone (301) 328-3956.

Washington University Medical School: First Annual Update Course in Ophthalmology

The Washington University Medical School: First Annual Update Course in Ophthalmology, sponsored by the Retina Research & Development Foundation and the Ophthalmology Department, will be held Sept. 22 and 23, 1989. For further information, write Kathy Ryan, Box 8096, 660 S. Euclid Ave., St. Louis, MO 63110; telephone (314) 362-5722.

West Virginia University: Tenth Annual Ophthalmology Conference

The West Virginia University: Tenth Annual Ophthalmology Conference will be held Sept. 22 and 23, 1989, at Sheraton Lakeview Resort and Conference, Morgantown, West Virginia. Frederick T. Fraunfelder will be the Hutchinson Lecturer. For more information, write Department of Ophthalmology, West Virginia University School of Medicine, Morgantown, WV 26505; telephone (304) 293-3757.

Tampa General Hospital and the University of South Florida: Seventh Annual Advanced Neuroradiology Seminar

The Seventh Annual Advanced Neuroradiology Seminar of Tampa General Hospital and the University of South Florida will be held at the Hyatt Regency Grand Cypress Hotel in Orlando, Florida, Oct. 26–28, 1989. For further information, contact Agnes Bridges, Radiological Services, Tampa General Hospital, P.O. Box 1289, Tampa, FL 33601; telephone (813) 251-7778.

University of North Carolina-Chapel Hill: Ophthalmology Residents' Day

The University of North Carolina-Chapel Hill: Ophthalmology Residents' Day, sponsored by the Department of Ophthalmology, will be held Dec. 2, 1989, in Chapel Hill, North Carolina. For further information, write Ms. Christine C. Cotton, Department of Ophthalmology, CB #7040, 617 Clinical Sciences Building, University of North Carolina, Chapel Hill, NC 27599.

South Carolina/North Carolina Societies of Ophthalmology: 1989 Annual Scientific Session

The South Carolina/North Carolina Societies of Ophthalmology: 1989 Annual Scientific Session will be held at the Omni Hotel, Charleston, South Carolina, Oct. 12–14, 1989. For further information, write Debbie Shealy, SC Society of Ophthalmology, P.O. Box 11188, Columbia, SC 29211; telephone (803) 798-6207.

Doheny Eye Institute: 21st Annual Meeting

The Doheny Eye Institute: 21st Annual Meeting will be held Sept. 21 and 22, 1989, at the Doheny Eye Institute, Los Angeles. For further information, write Dave Carpenter, Coordinator CME, 1355 San Pablo St., Los Angeles, CA 90033; telephone (213) 224-5580.

Second International Conference on Pneumatic Retinopexy

The Second International Conference on Pneumatic Retinopexy will be held Oct. 6 and 7, 1989, at Wyndham Harbour Island Hotel, Tampa, Florida. For further information, write Teri Tanase, c/o U. Sanderson Grizzard, M.D., 2655 Swann Ave., Suite 100, Tampa FL 33609; telephone (813) 875-6373.

Georgetown University School of Medicine: Outpatient Ophthalmology 1990

Georgetown University School of Medicine: Outpatient Ophthalmology 1990 will be held Oct. 13 and 14, 1989, at The Greenbrier, White Sulphur Springs, West Virginia. For further information, write Office of Continuing Medical Education, Georgetown University Medical Center, 3800 Reservoir Rd., N.W., Washington, DC 20007; telephone (202) 687-8735.

Wilmer Institute: Second Annual Current Concepts in Ophthalmology

The Wilmer Institute: Second Annual Current Concepts in Ophthalmology will be held Dec. 7–9, 1989, at the Thomas B. Turner Building, Johns Hopkins Medical Institutions, Baltimore, Maryland. For further information, write Johns Hopkins Medical Institutions, Office of Continuing Education, Turner Building, 720 Rutland Ave., Baltimore, MD 21205; telephone (301) 955-2959.

Puerto Rico Ophthalmological Society: Annual Ophthalmological Convention

The Puerto Rico Ophthalmological Society: Annual Ophthalmological Convention will be held Nov. 17–20, 1989, at the Hyatt Cerromar Hotel and Casino, Dorado, Puerto Rico. For information, wirte Victor M. Diaz Bonnet, M.D., Box 1184, Hato Rey, PR 00919; telephone (809) 765-9470.

Sainte-Justine Hospital: 14th Annual Pediatric Ophthalmology Day

The Sainte-Justine Hospital: 14th Annual Pediatric Ophthalmology Day will be held Oct. 13, 1989, in Montreal, Quebec. For further information, write Jean Milot, M.D., Chairman of the Scientific Program, Hospital Sainte-Justine, 3175 Cote Sainte-Catherine, Montreal, Quebec H3T 1C5; telephone (514) 345-4715.

St. John's Hospital and Health Center—Santa Monica: Current Trends in Vitrectomy Course

The St. John's Hospital and Health Center—Santa Monica: Current Trends in Vitrectomy Course will be held Sept. 15 and 16, 1989, at the Century Plaza Hotel, Los Angeles. An additional "Hands-On Only" session will be held Sept. 17. For further information, telephone Carla Johnstone at (213) 829-9034.

Pittsburgh Ophthalmology Society: New Officers

Bernard H. Doft, clinical associate professor of ophthalmology at the University of Pittsburgh School of Medicine, has been elected president of the Pittsburgh Ophthalmology Society for a two-year term. John S. Kennerdell, clinical professor of ophthalmology of the University of Pittsburgh School of Medicine, is president-elect.

Bausch & Lomb InVision Institute: 1989 Research Grant Recipients

The Bausch & Lomb InVision Institute 1989 research grant recipients are Ramesh Tripathi, University of Chicago; Normand Richard, National Vision Research Institute, San Diego; and Charles Connor, Southern College of Optometry, Memphis. Awardees share $25,000 grant funding in the field of contact lenses.

Food and Drug Administration: Sunglass Labeling

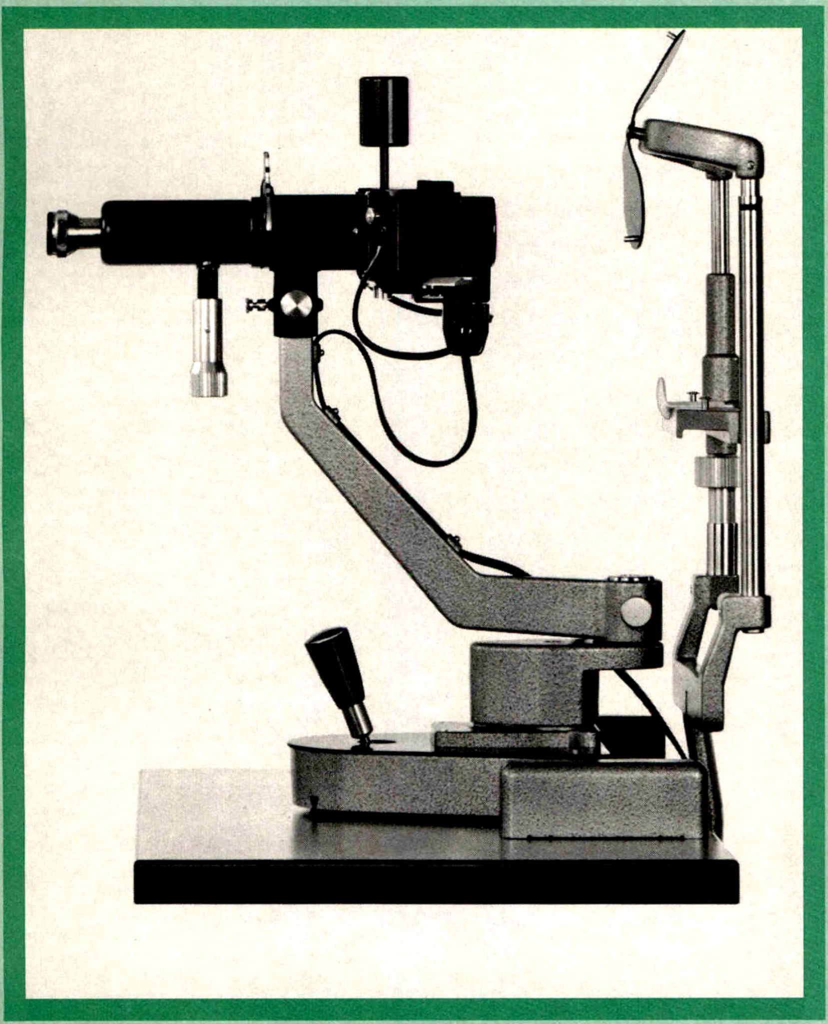
The Food and Drug Administration announced May 15, 1989, a voluntary labeling program developed by the Sunglass Association of America and the Food and Drug Administration. Under the labeling program abbreviated information giving the amount of ultraviolet light absorbed is attached directly to sunglasses. A brochure now being prepared, will be available at stores to describe the appropriate uses of various lenses.

Cosmetic sunglasses are lightly tinted and block at least 70% of sunlight ultraviolet B (290–320 nm) and 20% of ultraviolet A (330–400 nm) radiation and less than 60% of visible light. They are recommended for use in nonharsh sunlight activities. General purpose sunglasses block at least 95% of ultraviolet B radiation and at least 60% of ultraviolet A radiation and from 60% to 92% of visible light. They are recommended for most uses in a sunny environment such as boating, driving, flying, or hiking. Their shades range from medium to dark color. Special purpose sunglasses block at least 99% of ultraviolet B radiation and 60% of ultraviolet A radiation. They block no more than 97% of visible light. They are recommended for activities in very bright environments such as ski slopes and tropical beaches. The Food and Drug Administration cautions that lenses that block more than 92% of visible light are not recommended even for driving in daylight because of difficulty in seeing traffic signals. Sunglasses should never be used when light levels are too low for adequate visibility.

The Food and Drug Administration said sunglasses should not be relied upon for protection against artificial sources of ultraviolet such as tanning lamps or the lights in tanning booths. Even closed eyelids are not sufficient protection from the penetrating ultraviolet light used in tanning, so special goggles are required.

There is no warning concerning the danger of wearing sunglasses for night driving.

Haag-Streit Ophthalmometer



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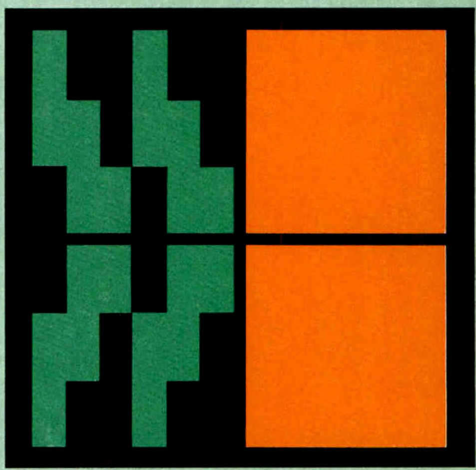

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NEW PRODUCTS AND SERVICES

New products and services considered by the editors to be of interest to our readers are described on the basis of information supplied by the companies cited. Publication of these notices does not imply endorsement or warranty by The Ophthalmic Publishing Company, publishers of The American Journal of Ophthalmology, for these products and services.

▶ Diagnostic Equipment

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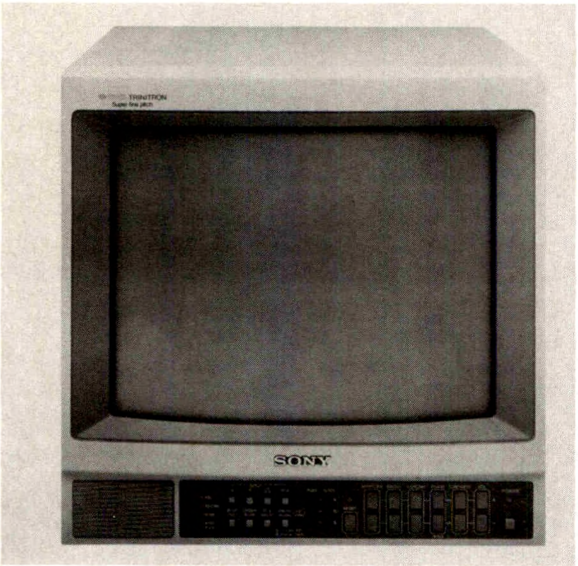

Sony Medical Electronics Division has introduced the PVM-1343 MD, a 700 TV line color video monitor designed specifically for medical applications. The 13-inch monitor accepts most standard videographic signals and delivers sharp, detailed images using Sony's Super Fine Pitch Trinitron technology. The monitor features a variety of input capabilities, multisystem color standards (PAL, SECAM, NTSC 3.58, and NTSC 4.43), automatic white balance adjustment circuitry, and an underscan mode.

Nikon Inc.
Instrument Group
Ophthalmic Department
19601 Hamilton Ave.
Torrance, CA 90502-1309
Tel: (213) 516-7124

As part of its new systems approach to eye care and testing, Nikon has introduced the new compact OT-7A Auto Optester for measuring subjective refraction. The new device can be easily integrated with other test instruments for added versatility. The OT-7A is a remote-controlled device and provides increased precision in ocular examinations. All operations can be run from the keyboard of a remote control console, including power controls for convergence, pupillary distance, and prism measurement. Examinations are possible in three modes (Far 1, Far 2 and Near), retaining the data from one mode after switching to another.

Seikosha America Inc.
1111 Macarthur Blvd.
Mahwah, NJ 07430
Tel: (201) 529-4655

The Seikosha VP-3500 video printer provides high-resolution 64-tone gray-scale prints for diagnostic hard copies used in such medical disciplines as radiology, cardiology, ophthalmology, obstetrics, and orthopedics. That means an improved resolution of up to 1,280 lines, and a line rate high enough for magnetic resonance imaging, computed tomography and catheterization laboratory requirements. The prints are on synthetic thermal paper so that the images can last for years.

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Northboro, MA 01531
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(508) 393-5726 (Massachusetts)

Interzeag Inc., the authorized sales and service company for the Octopus Automated Perimeters, announced that it has a new brochure for the Octopus 500EZ automated perimeter. The brochure will assist eye care professionals in understanding the Octopus and the personal computer software that accompanies the system. The brochure is available free of charge.

Intraocular Lenses

Iolab Intraocular
500 Iolab Dr.
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Iolab Models 85J and 2100 anterior chamber lenses have been determined safe and effective by the Food and Drug Administration. Model 85J is a flexible, four-point fixated anterior chamber lens with accentuated footplates on each haptic. The footplates help visualize placement of the lens in the anterior chamber and decrease the potential for anterior synechia encapsulation. Sizing of the 85J is made easy by a flexible haptic design that minimizes pressure against ocular tissue. The lens is available in small, medium, and large sizes.

Model 2100, designed in cooperation with Charles Kelman, M.D., is a flexible three-point fixated anterior chamber lens. The inferior haptic has the same accentuated footplates as the 85J, but the superior haptic has a single positioning hole to assist with insertion. Sizing of the Model 2100 is made simple by its flexible design. It is available in small and large sizes.

3M Vision Care
3M Center
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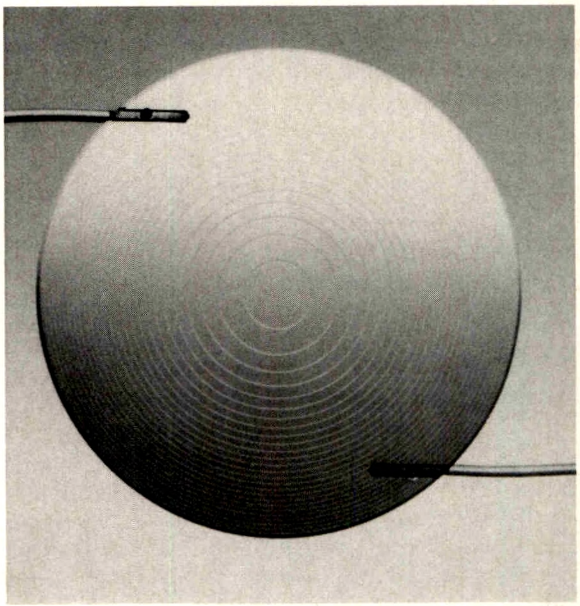
Tel: (612) 736-3524



The 3M Multifocal intraocular lens, currently limited by U.S. law to investigational use, is designed to mimic normal vision and to minimize the chance that the person will need bifocals or spectacles after cataract surgery. This lens relies on diffractive optics, which when used in conjunction with refractive optics, evenly distributes light to two focal points—one for near vision, the other for distance vision. On its posterior side, the 3M lens has a series of diffractive rings that are characterized by tiny steps. Correction for distance vision is made by conventional refraction on the anterior side of the lens. The diffractive posterior surface gives a second focus, which provides for near vision. Contraindications with the implant do not differ from those of a conventional, single focus intraocular lens.

▶ Surgical Instruments

American Surgical Instruments Corp.
806 Burr Oak Dr.
Westmont, IL 60559
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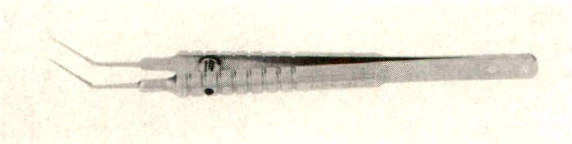
(312) 986-8032 (Illinois)



The Capsulorhexis Forceps, introduced by American Surgical Instruments Corp., allows the surgeon to perform a circular-tear capsulotomy. The forceps has 11-mm long jaws with a recessed space inbetween for inadvertant pickup of iris. The triangular, sandblasted tips of the forceps is set at a 45-degree angle for picking up the anterior capsule. The Capsulorhexis Forceps features a round handle that facilitates maneuverability to tear the capsule in a round fashion. Catalogue no. AE-4394.

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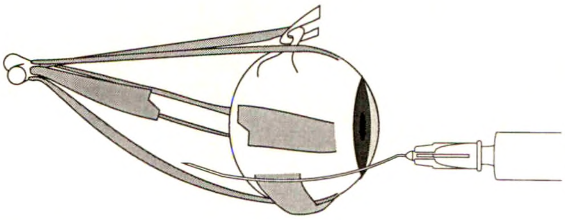

Visitec has introduced a specialized curved design retrobulbar needle. The 5019 Retrobulbar Needle (Straus) has all the advantages of a retrobulbar injection, but has improved safety. The needle is partially curved to minimize global penetration and to allow easier positioning in the muscle cone. The straight end of the distal needle portion is used to minimize damage to the optic nerve, optic nerve sheath, and blood vessels. The needle is also designed with a blunt Atkinson tip. The retrobulbar needle is 25 g $\times$ 1 3/8″ (0.51 $\times$ 34 mm), and is protected with a specially designed sheath and sterile packed.

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▶ Diagnostic Devices

The Fresnel Prism & Lens Co.
Route 1, Box 298-3
Siren, WI 54872
Tel: (800) 544-4760

The Fresnel Prism Trial Set includes seven thin, lightweight, acrylic prisms of 12, 15, 20, 25, 30, 35 and 40 diopters, which are up to $^{1}/_{10}$ the thickness and weight of conventional equivalent power prisms. Prism rings fit all standard trial frames and clip-ons. These features combine to provide quick, convenient changes for diagnostic and therapeutic procedures. The high optical quality prisms are ideal for evaluating potential prospects for fusion and surgical success preoperatively, enhancing surgical results postoperatively, fusion stimulus in other muscle deficiencies, and alleviating diplopia in sudden-onset strabismus. The price of the trial set is $125.

▶ Contact Lenses

Allergan Optical Inc.
2525 Dupont Dr.
Irvine, CA 92713
Tel: (714) 458-5136

Allergan Optical introduced a bifocal soft contact lens that uses high-tech optics and precision manufacturing techniques to provide vision for patients with presbyopia. The Hydron Echelon lens, a diffractive soft bifocal contact lens, has been cleared for marketing in the United States. The lens is easy to fit, provides good visual acuity, is comfortable, and can be prescribed for a large variety of patients. Diffraction splits the light as it passes through the lens' optic zone and provides two distinct near and distance focal points. By using principles of diffraction to create a full aperture, simultaneous vision lens, the Hydron Echelon lens is virtually pupil-size independent.

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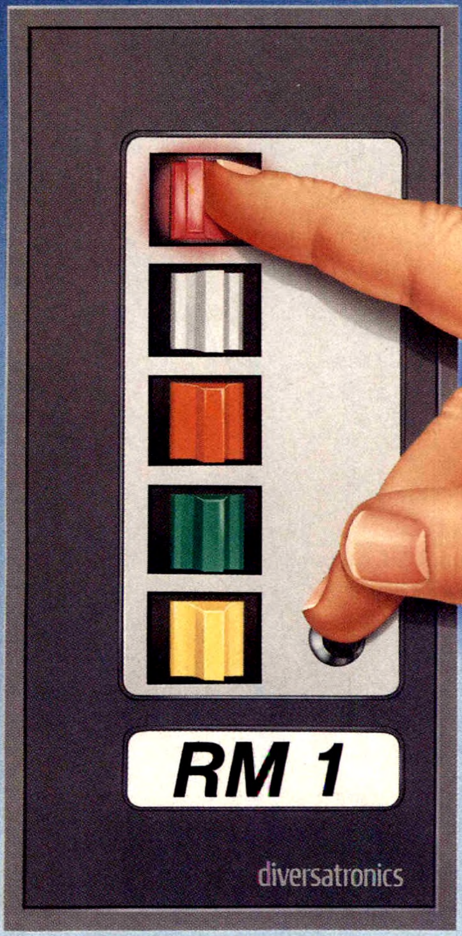

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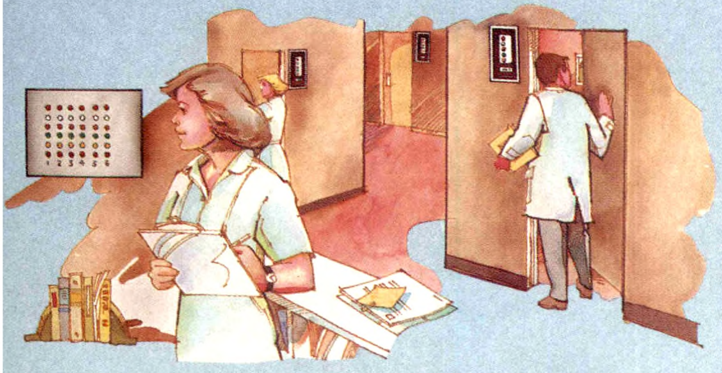

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Positron Emission Tomography to Study the Effect of Eye Closure and Optic Nerve Damage on Human Cerebral Glucose Metabolism

Motohiro Kiyosawa, M.D., Thomas M. Bosley, M.D., Michael Kushner, M.D., Dara Jamieson, M.D., Abass Alavi, M.D., Peter J. Savino, M.D., Robert C. Sergott, M.D., and Martin Reivich, M.D.

We used ^{18}F-2-fluoro-2-deoxyglucose and positron emission tomography to evaluate the effect of visual deprivation on brain glucose metabolism. In experiment 1, we compared local cerebral metabolic rates for glucose in seven normal volunteers studied with eyes closed to 11 age- and sex-matched normal volunteers studied with eyes open. Whole brain metabolism was similar in the two groups, and region/whole brain analysis of metabolic data showed that metabolism in the calcarine posterior cortex was decreased by 14% ($P < .05$) with eye closure. Glucose metabolism in other regions was not different between the two groups.

In experiment 2, we compared glucose metabolism in six patients with severe bilateral optic neuropathies to 12 age- and sex-matched normal controls. Whole brain glucose metabolism was unchanged in the optic neuropathy group compared to controls. However, statistically significant reductions in glucose metabolism in the optic neuropathy group were found in anterior calcarine cortex (17%), posterior calcarine cortex (27%), peristriate cortex (27%), and lateral occipital cortex (15%). The metabolic effects of damage to the pregeniculate visual system went well beyond those of simple eye closure.

Custom Orbital Implant in the Repair of Late Posttraumatic Enophthalmos

Allen M. Putterman, M.D., and Arthur L. Millman, M.D.

We repaired late, posttraumatic enophthalmos in 21 patients by inserting a large, soft, Silastic block through a lower eyelid flap and transconjunctival approach to the orbit. These blocks were hand carved at the time of surgery to match bony defects as characterized by hypocycloidal tomographic biometry. Enophthalmos and hypo-ophthalmos were ameliorated with acceptable appearance in all cases. No implant rejections, migrations, or infections were found. Complications included upper eyelid blepharoptosis, lower eyelid retraction, and conjunctival prolapse. The improvements were stable over a median follow-up of 13 months.

Medial and Lateral Wall Decompression for Thyroid Ophthalmopathy

Charles R. Leone, Jr., M.D., Ken L. Piest, M.D., and Richard J. Newman, M.D.

A two-wall decompression of the orbit, consisting of removal of the medial and lateral walls, was successful in eight patients with thyroid ophthalmopathy. The lateral wall was by removed by using the standard orbitotomy technique in addition to enlarging the space with a pneumatic burr, and the medial wall was removed through a direct medial canthal incision. Two patients had optic neuropathy, one had intermittent subluxation of the globe, and five had symptoms of exposure or increased pressure in the orbital area. In our eight patients, the two with optic neuropathy improved, the patient with subluxation of the globe became asymptomatic, and the other five had less exposure and were more comfortable. The amount of decompression ranged between 4 and 7 mm. The lacrimal sac was injured in one patient; temporary silicone intubation avoided any permanent sequela.

Angiolymphoid Hyperplasia With Eosinophilia of the Orbit Associated With Obstructive Airway Disease

Scott B. Sheren, M.D., Philip L. Custer, M.D., and Morton E. Smith, M.D.

Two patients with angiolymphoid hyperplasia with eosinophilia isolated to the orbit had eyelid swelling, a superior orbital mass, and histories of intermittent obstructive airway disease. One patient later developed a transient peripheral blood eosinophilia as high as 36%. One lesion recurred 38 months postoperatively and responded to systemic corticosteroid therapy.

INSTRUCTIONS TO AUTHORS

For the preparation of typescripts for THE AMERICAN JOURNAL OF OPHTHALMOLOGY

For more detailed information, see the Instructions to Authors published periodically in each volume, or write to Editorial Correspondent, American Journal of Ophthalmology, Tribune Tower, Suite 1415, 435 N. Michigan Avenue, Chicago, IL 60611.

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CBE Style Manual Committee: Council of Biology Editors Style Manual. A Guide for Authors, Editors and Publishers in the Biological Sciences, 5th ed. Bethesda, Council of Biology Editors, 1983.

The Chicago Manual of Style, 13th ed. Chicago, University of Chicago Press, 1982.

Strunk W., Jr., and White, E. B.: The Elements of Style, 3rd ed. New York, Macmillan Publishing Co., 1979.

Treatment of Postvitrectomy Fibrin Pupillary Block With Tissue Plasminogen Activator

Glenn J. Jaffe, M.D., Hilel Lewis, M.D., Dennis P. Han, M.D., George A. Williams, M.D., and Gary W. Abrams, M.D.

We injected 25 μg of recombinant tissue plasminogen activator into the anterior chamber or the vitreous cavity in seven aphakic patients for pupillary block caused by a complete fibrin pupillary membrane that formed after vitrectomy with fluid-gas exchange. Progressive fibrin deposition resulted in pupillary block by three days after vitrectomy surgery in six patients, and seven days after vitrectomy in one patient. The pupillary block was associated with increased intraocular pressure in six patients. Tissue plasminogen activator was injected via the corneoscleral limbus in five patients and via the pars plana in two patients. In all patients, injection of tissue plasminogen activator resulted in complete fibrinolysis of the fibrin pupillary membrane within four hours, associated with a deepening of the anterior chamber. In the six patients with increased intraocular pressure at the time of tissue plasminogen activator injection, dissolution of the fibrin membrane was associated with a decrease in pressure. In all patients, intraocular pressure had returned to normal by three days after the injection. No complications were associated with the injection.

© American Journal of Ophthalmology 108:170–175, August, 1989

Fibrovascular Proliferation and Retinal Detachment After Intravitreal Injection of Activated Macrophages in the Rabbit Eye

Yan-Nian Hui, M.D., Randi Goodnight, B.Sc., Nino Sorgente, Ph.D., and Stephen J. Ryan, M.D.

Injection of activated macrophages into the posterior vitreous of the rabbit induced vigorous fibrovascular proliferation over the optic disk and medullary rays, as demontrated by ^{3}H-thymidine autoradiography. One week after injection, endothelial cells and pericytes of the capillaries near the inner surface of the optic disk and rays were labeled; fibroblast-like cells, which were also labeled, migrated and formed vitreous strands. By the second week after injection, the fibrovascular tissue proliferated most actively, and traction medullary ray detachment and peripapillary retinal fold formation were observed. The cellular proliferation was accompanied by inflammatory cell infiltration. Glial cells within the optic disk, as well as retinal pigment epithelial cells beneath the detached retina, were labeled by ^{3}H-thymidine. These results demonstrate that the fibrovascular proliferation originates from the vessel complex of the optic disk and medullary rays in this experimental model of retinal detachment.

© American Journal of Ophthalmology 108:176–184, August, 1989

Decreasing Frequency of Enucleation in Patients With Retinoblastoma

Jerry A. Shields, M.D., Carol L. Shields, M.D., and Varunan Sivalingam, M.D.

We reviewed our 15-year experience with the management of 324 cases of retinoblastoma. There has been a definite trend away from enucleation in both unilateral and bilateral cases during recent years. In cases of unilateral retinoblastoma, the affected eye was salvaged in 4% of cases (two of 49) during the five-year interval from 1974 through 1978, in 14% of cases (seven of 50) from 1979 through 1983, and in 25% of cases (20 of 80) from 1984 through 1988. In cases of bilateral retinoblastoma, both affected eyes were salvaged in 4% of cases (one of 24) from 1974 through 1978, in 18% of cases (nine of 50) from 1979 through 1983, and in 25% of cases (18 of 71) from 1984 through 1988. Earlier diagnosis of retinoblastoma and refinements in conservative methods of management are believed to be the main reasons for this trend away from enucleation.

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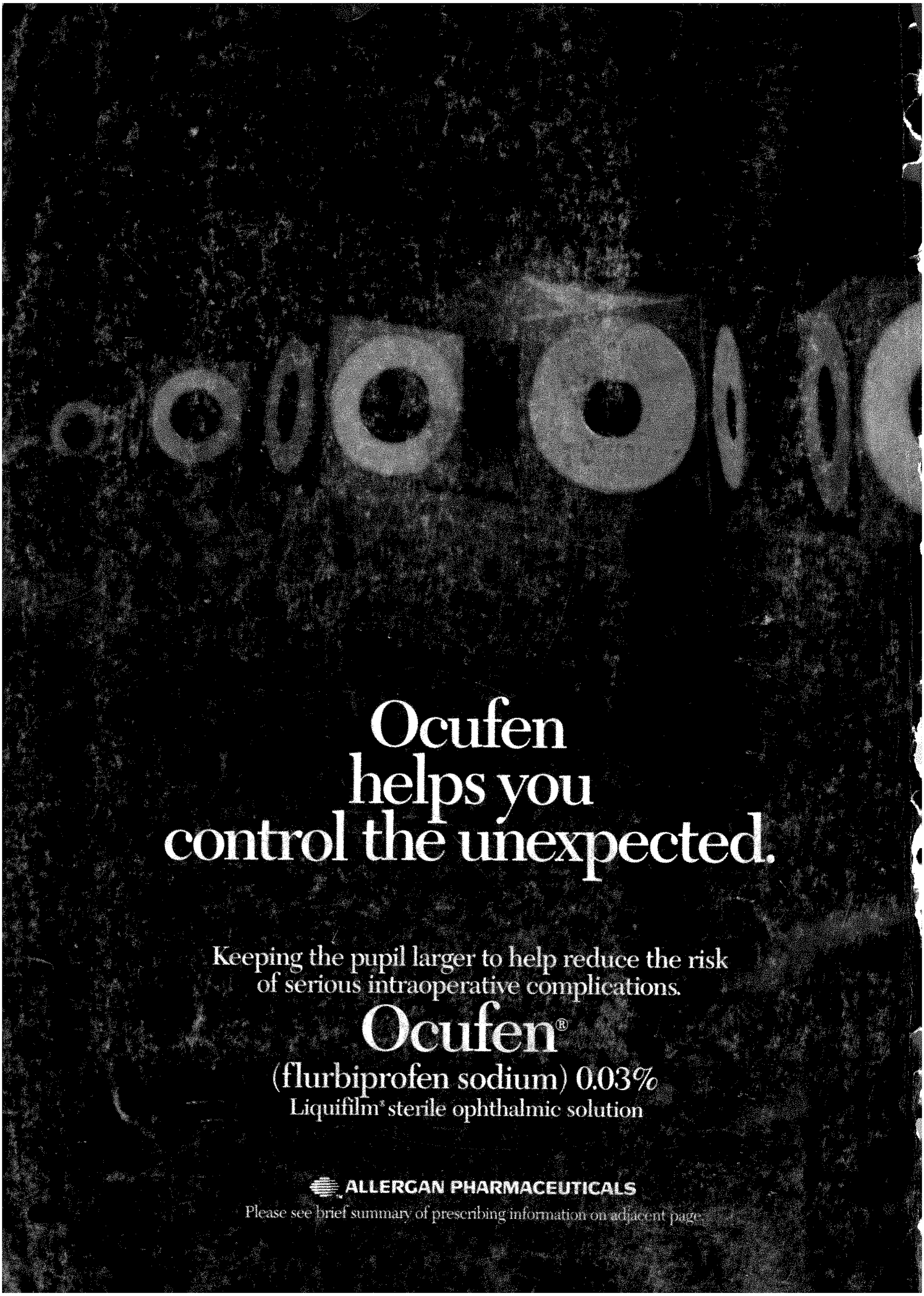
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